SUBMISSION

to the

HOUSE OF COMMONS SPECIAL COMMITTEE

ON DRUG COSTS AND PRICES

by the

PHARMACEUTICAL MANUFACTURERS

ASSOCIATION OF CANADA

at

OTTAWA, ONTARIO

JUNE, 1966

PMAC

Pharmaceutical Manufacturers Association of Canada
1110 Gillin Building • 141 Laurier Avenue West • Ottawa 4, Ontario

House of Commons Special Committee
on Drug Costs and Prices
Government of Canada

June 1st, 1966.

Mr. Chairman and Members:

This submission is presented to the Committee by the Pharmaceutical Manufacturers Association of Canada, a non-profit organization founded in 1914 and incorporated under the Dominion Companies' Act in 1959.

The Association represents 57 companies engaged in manufacturing and distributing ethical pharmaceutical preparations in Canada. The term "ethical" refers to pharmaceuticals dispensed on doctors' prescription and those not advertised to the public, as opposed to proprietary or patent medicines which are so advertised. Some of our member companies also make proprietary medicines, but our Association does not represent this field of medication.

Attached to this submission under Appendix O is a list of our member companies.

Our delegation to the Committee is composed of the following persons: Mr. R.F. Daily, Chairman of the Board of PMAC; Mr. E.G. Gregory, Vice-Chairman of the Board; Mr. H.D. Cook, Immediate Past Chairman of the Board; Mr. Roger Larose, Vice-President, Ciba Company Limited; Mr. Peter Howsam, Vice-President and General Manager, Warner-Chilcott Laboratories Co. Limited; Dr. Brian Stewart, Director, Pharma-Research Canada Limited; Mr. Gordon F. Henderson, Patent Consultant; Mr. Fred Hume, Q.C. and Mr. Gregory Gorman, Legal Consultants; Dr. Peter C. Briant, Vice Dean and Director, School of Commerce, McGill University, Consulting Economist; Dr. Arthur Grieve, Director - Quality Control, Ayerst Laboratories; and myself as President of the Association.

In preparing this submission, we have attempted to follow the Committee's terms of reference and, at the same time, offer the Committee as complete an understanding as possible of the role of our pharmaceutical manufacturing industry in the economy and health services of Canada. It is our hope that the contents will be of assistance to you in your deliberations.

Respectfully submitted,

Wm. W. Wigle

Wm. W. Wigle, M.D., C.M.,
President.

P R E A M B L E

a prefatory statement

by

Dr. William W. Wigle, President

Pharmaceutical Manufacturers Association
of Canada

My colleagues and I in PMAC have addressed ourselves to the question of the present level of drug prices in this country. We gave long and careful consideration to the peculiarities of ethical drug manufacturing that make this industry unique of its kind. Our deliberations, on the evidence adduced in the main body of this brief and documented in the appendices, impelled us to the fundamental conclusion that the cost of drugs to Canadians is fair and reasonable. The plain fact is that if we consider the real cost of any product or service — the hours of labour necessary to earn the money for the purchase — we find that Canadians come off well in terms of the pharmaceuticals necessary to our national health and well being. A Canadian citizen is obliged to work fewer hours than the peoples of most other countries for the ethical drugs needed for the maintenance of his and his family's health.

Our recognition of this fact, however, has not deterred us from exploring every conceivable means of reducing the prices of pharmaceuticals to Canadians. As good corporate citizens, our member companies have expressed their willingness to work with responsible government authorities in seeking sensible means of lowering drug costs and prices to the people of Canada, along the lines suggested in the principles advanced by the Association and outlined in the body of this brief. And as sound business people, the chief executives of our member firms are well aware of the advantages that can accrue to any company able to pare its costs and its prices in a highly competitive industry. But there are stern realities that must be faced by any company doing business in Canada, as well as certain characteristics of drug manufacturing that must be carefully considered. I should like to review these briefly for the Committee.

First of all, the costs involved in the producing of pharmaceuticals tend to be higher than they ordinarily would be because of the need for building quality into the product through every stage in the manufacturing process. The reasons for this should be obvious. It is not simply a matter of building a better mousetrap: it is in fact a matter of safety. Within the past three decades the use of pharmaceuticals has loomed ever larger in the practice of medicine, and the drugs themselves have become more and more potent and complex. The high costs of quality control necessary to ensure the availability of drugs that are of the required safety, strength, and therapeutic effectiveness influence every facet of the manufacturing process. Because we are, after all, concerned with supplying the means to relieve human suffering and to treat and to cure those conditions that have plagued mankind over the centuries, we must continually pay a premium to make sure that our products perform these functions. Any company that cuts corners on the matter of quality control does so at its peril.

Our distribution costs are far higher than we like them to be. This is, of course, partly owing to the geographic facts of Canadian life. High quality pharmaceuticals must be readily available to all physicians no matter where they may be practising in Canada, to all hospital dispensaries, and to the vast network of pharmacies that serve a great and thinly-populated country. The costs associated with controlling the distribution of fragile, and in many instances, perishable, pharmaceuticals are real enough for any manufacturer, but to those must be added the record-keeping costs of the increasing number of drugs that the physician now has at his disposal.

Our costs of marketing are high. And this is a matter of concern to the members of our industry and to me personally. But this is one aspect of

the industry's economics that is most difficult to control. Our member companies do not advertise to the general public: they inform the medical profession of the availability of new pharmaceuticals. And while introductory and reminder advertising in professional publications make up a sizeable item in the marketing budget of every drug manufacturing company, by far the heaviest marketing expense that must be borne is the cost associated with sending highly-trained professional representatives into the field to make our medical people aware of the existence of new drugs, of their indications and contra-indications, of their side effects and therapeutic potential. We would like to reduce these costs and we will propose a recommendation to this effect presently, among the other recommendations we are prepared to make to this Committee.

But the greatest concern, without question, is the matter of pharmaceutical research and the patent position of the pharmaceutical manufacturer in Canada. This is a research-based industry that spends internationally something in the order of half a billion dollars a year to provide us with the new life-saving drugs that have in the past two decades all but revolutionized the practice of medicine. Better than ninety per cent of the drugs prescribed today were unavailable twenty short years ago. And yet the irony is that some of the life-saving and curative pharmaceuticals that I have the privilege of prescribing today will never earn a dime for the companies that developed them. There are a couple of searching reasons for this state of affairs. In the first place, some of these discoveries have been products of other intensive research programs, results, as it were, of a total research

activity. In this instance the man in the street gains because our companies give these drugs that cure rare diseases to our doctors and hospitals either at factory cost or free of charge. And again, the company that spent perhaps $5 million developing a new drug may not fully recover its investment if, after developing the new product and creating a Canadian market for it, an imitating company infringes its patents or secures a manufacturing licence for a token royalty.

And this, it seems to me, is the nub of the problem that faces Canada at the present time. In recent years the Hall Commission and the Restrictive Trade Practices Commission have suggested that the abolition or sharp reduction of patent protection is a necessary move to reduce the cost of prescribed drugs. I can think of no more misguided step for the government of this country to take. Canada can not have a free ride. If we stand to one side and wait for the United States or Europe to develop new drugs with the notion that we will then import them, we may wind up paying more than we should for questionable products and we will wait longer to receive them. We must pay our way. The cost of pharmaceutical research is a fact of twentieth century life.

We have, perhaps, devoted what might be considered a disproportionate amount of time to consideration of the patent position of this industry. In my judgment it is called for. Our patent law should encourage swift and full disclosure of new pharmaceutical developments. And it should reward those companies or individuals that are willing to invest time and huge sums of money in Canada's medical future. At the present time one large international pharmaceutical company, Ayerst, McKenna

and Harrison, is doing all of its continental research in Montreal. Other companies, for example, Pharma-Research Canada Limited, Bristol Laboratories, Smith Kline & French and Warner-Lambert have built new laboratories in Canada to continue this trend. Still others of our member companies have begun to expand their research facilities. But if this trend is to continue, we must foster the incentive that gave rise to it in the first place. Above all, we must not set up conditions that would destroy that incentive. The cost of drugs, whether we like it or not, is very closely linked to the maintenance of laboratories that will provide new drugs. If Canada is to do its share in helping to establish new beach-heads in the eternal conquest of disease, it must foster the conditions that will enable the drug industry to grow and flourish in this country and throughout the world.

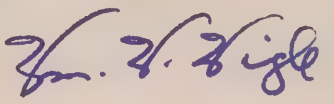
We have some recommendations to make. They are not startling, but they will, if adopted, reduce the cost of drugs to Canadians without damaging an essential industry. Our principal recommendations are these: abolition of the federal sales tax on prescription drugs; a wider availability of drug insurance to prevent catastrophic drug expenses during medical emergencies; and the establishment of an independent source that would provide doctors and pharmacists with accurate and up-to-date information about pharmaceutical products and their prices. And because of the vital importance of safety and reliability of the drugs Canadians receive, we make the further recommendation that a properly qualified tribunal be established to decide the merits of compulsory licence applications from would-be

secondary manufacturers. If we are to reduce the cost of drugs, we must not do so at the expense of the very health of the industry itself or to the hazard of the consumer.

I should like to close my remarks with two thoughts that I believe are worthy of this Committee's consideration. The first is that during my years with the Ontario Medical Association and the Canadian Medical Association my greatest preoccupation was with the quality of the medical care being received by Canadians. I am more convinced than ever now of the vital link between high quality pharmaceuticals and effective medical care. And I wish that during those years I had been aware of the problems that beset this industry and the dangers that threaten therapeutic advances. I would have strongly urged all of the support I could have mustered to help solve the difficulties of an industry on which my profession at this point leans very heavily.

And finally, my investigation of this industry has convinced me that the use of the products of responsible, research-oriented drug makers is a positive contribution to new cures, remedies, and disease prevention. In almost every study we look at in relation to the safety, effectiveness and purity of drugs, we reach the common conclusion that the greatest guarantee of quality rests in the integrity of the manufacturer.

With these thoughts our brief is respectfully submitted.



Wm. W. Wigle, M.D., C.M.,
President.

SUMMARY

Section 1— Introduction

The make-up of PMAC and the characteristics of the industry are described in terms of its economic challenges and social responsibilities.

Section 2— Breakdown of the Prescription Dollar

This section presents the various elements involved in the cost of prescription drugs.

Section 3— Economic Structure of the Drug Industry

Surveys carried out by PMAC among its member companies indicate the size of the prescription drug market, how the market is shared, the extent to which the manufacturing activity is primarily Canadian, the market's growth, and the industry's composition and profit picture. The survey results also demonstrate the industry's direct investment in the Canadian economy and its role as a taxpayer.

Section 4— The Cost of Drugs to Canadians

The real cost of drugs to Canadians is compared to the cost of drugs to the citizens of other countries, not in terms of translating foreign currencies into Canadian dollars, but in terms of the standards of living and the earning powers of the peoples in the countries compared. The results show that Canadians can buy their drugs with less labour than people in most other countries.

Section 5— Distribution and Pricing

Peculiarities of distribution that are characteristic of Canada are described, along with pricing considerations that are influenced by the

industry's sales patterns to governmental customers, and to wholesale and retail outlets.

Section 6—The Cost of Manufacturing and Quality Control

This section employs survey figures to isolate the costs of manufacturing, and the added costs required for effective quality control.

Section 7—The Cost and Value of Research

The mounting expenses involved in the discovery and synthesis of new compounds and the steps that must be taken to bring a new drug to market, along with the cooperative and competitive aspects of research are discussed, together with considerations of the growing scientific maturity of Canada, and the expenditures necessary to bring the fruits of international pharmaceutical research to Canadians.

Section 8—Public Service Products

This is a description of the products that are vital in the treatment of rare diseases and are made available to physicians either free of charge or at factory cost. The sales potential of these products is so slight that their development and manufacturing costs could not be recovered unless they were spread over a company's total product spectrum.

Section 9— The Cost of Marketing

The costs of physicians' information are broken down and the geographical facts of doing business in Canada are outlined. The provision of scientific information is differentiated from the product promotion associated with most industries, and the measures necessary to inform the medical profession of new indications or contra-indications are set

forth. Extensive reviews are made of the purposes and costs of detailing, pharmaceutical mail and journal advertising, both in this section and in the appendices. The high cost of introducing new products is explained, along with PMAC's proposal to establish an independent and properly coordinated drug information system in this country.

Section 10— The Cost of Safety

This contains a review of the costs of safety and its overall influence on the costs of research, manufacturing, marketing and distribution.

Section 11— Pharmaceutical Patents

If quality, safety and therapeutic effectiveness are to loom larger than price alone as criteria for the purchase of pharmaceuticals, the cost of drugs in Canada must be related to the patent situation. This section describes the origin of Section 41(3) of the Patent Act and the problems created by the way it is interpreted and administered; the necessity for patent protection as a research and investment incentive; the misunderstanding on which the establishment of royalties has been based; the dangers inherent in governmental encouragement of those who seek to produce pharmaceutical imitations; the opposing trend that is now manifest in Europe; and PMAC's patent recommendations, which include the establishment of a tribunal to decide on compulsory licence applications.

Section 12— The Question of "Generic Equivalency"

This section discusses the differences between non-proprietary or generic names and brand names, and it presents the arguments in favor of brand names that establish the manufacturers' responsibility for their own particular drug products. It considers the broad question of whether

any two drug products can be considered truly equivalent and points up the factors which can affect therapeutic efficacy.

Section 13—The Provision of Prescribed Drugs under Medicare and Welfare Programs

PMAC strongly believes that any assistance program proposed by government should enable doctors to prescribe medications solely on therapeutic considerations. The nine principles that PMAC feels should govern the provision of prescription drugs under health service programs are set forth.

Section 14—Recommendations Relating to the Cost of Drugs

PMAC has put forward seven recommendations, some of which would reduce the price of drugs generally, some of which would reduce the prices of certain products, and some of which would reduce prices to certain groups of citizens.

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B. PMAC's Principles of Ethics.

C. PMAC's Code of Marketing Practice.

D. The Role of the Detailman. (This appendix studies the functions and costs of professional representation of pharmaceutical companies to the medical profession.)

E. PMAC's Annual Statistical Survey Results for 1964.

F. International Drug Prices, a comparison of Canadian prices in domestic currency units and hours of labour with results for seven other countries.

G. The Cost of Quality Control.

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I. The Cost of Direct Mail.

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L. "Quality of Drugs." (An analysis of the section of the Hall Commission Report entitled "Quality of Drugs.")

M. What is a Generic Equivalent? (An article by three prominent physicians, reprinted from the magazine, American Professional Pharmacist.)

N. Pharmacare, a health service plan sponsored by CPhA to make high quality pharmaceuticals available to Canadians.

O. List of Member Companies of PMAC.

INTRODUCTION

This presentation is made on behalf of the Pharmaceutical Manufacturers Association of Canada. The PMAC has at present 57 members who produce about 85 per cent of the prescription drugs sold in this country. Under the by-laws of the Association there are two types of membership, and Appendix A is a PMAC application that outlines the classifications and membership requirements.

Currently, there are 52 full members and five associate members. It will be seen that all companies are required to meet proper conditions for control of quality and standards; ability to qualify under the Canadian Government Specifications Board regulations is a further requirement for membership.

In addition, each member must subscribe to a Code of Ethics and a Code of Marketing Practices. These are attached as Appendix B and Appendix C.

"Provision, Distribution and Cost of Drugs in Canada," a study made for the Royal Commission on Health Services by the Research and Statistics Division of the Department of National Health and Welfare, reports that in 1960 there were 198 establishments "engaged chiefly in the manufacturing of pharmaceuticals and medicines."

The following breakdown is given: "It seems that many of these 198 plants are small regional concerns, while others manufacture proprietary medicines exclusively. Probably more than two-thirds of the plants are what might be considered multi-line pharmaceutical

manufacturers. Approximately three-quarters are multi-line proprietary manufacturers. The remainder comprise agents, wholesalers and retailers who also manufacture some medicinals plus packaging concerns and other suppliers." (p.24) Many manufacturers have not sought to join our Association. So far as it is possible to judge from available information, many would not meet the rigorous standards that are a qualification of membership.

This presentation relates solely to prescription products: those available only on prescription, or designed primarily for sale on prescription, and so not advertised to the general public. These are the products referred to as human pharmaceuticals. However, some of these products can be bought from retail pharmacies by the public without prescription, and some companies have subsidiaries, affiliates or divisions which manufacture and sell proprietary medicines advertised to the public for self-medication. Most of the statistical information in this presentation has been developed for the prescription drug portion of the business alone, but, where company earnings are concerned, any separation must be arbitrary.

Our presentation is not intended to give a total picture of the operations of either the drug industry in Canada or our own Association. Rather it takes the question: "What are the reasons for the present level of drug prices in Canada?" and presents the answers as they appear to us, answers based on sustained experience of conducting a highly specialized business in this country.

Further, we believe it axiomatic that in a country which has attained

the general standard of living of Canada no citizen should go without needed medication because he cannot afford it. Our brief therefore concludes with certain recommendations which, we believe, will help ensure that every Canadian is able to obtain the drugs prescribed by his physician, and that these drugs meet the highest standards of safety, reliability and therapeutic effectiveness. We would caution against any consideration of drug costs which divorces them from these three essential qualities.

Characteristics of the Drug Industry

The prescription drug industry has its particular and significant characteristics:

1) When people buy drugs on prescription, they do not, themselves, decide what products they are to buy, or, therefore, how much the purchase will cost them. In addition, the need to make the purchase is in itself usually unwelcome;

2) The demand for prescription products as a whole is influenced primarily by the incidence of illness. This incidence combines with the medical assessment of comparative value to determine the sale of individual products; demand is relatively unresponsive to changes and differences in pricing;

3) The industry is composed of a large number of strongly competitive companies, yet the nature of their products requires a notable degree of responsibility in the conduct of competition;

4) Companies must meet a high level of relatively fixed costs. For instance, an effective research operation must be maintained even though it does not yield immediate products. Similarly, as explained in Appendix D, the costs associated with an effective physicians' information service must be borne even in the face of a decline in sales revenue;

5) Companies must ensure that all the products they market are available on a national basis, even though only limited revenues can be expected from many that are specifics for relatively rare illnesses and conditions. Similarly, full medical information must be provided about all products. This includes maintaining an advisory service for physicians, based on the latest world-wide scientific knowledge;

6) Although this is not a regulated industry in the technical sense, it is subject to a considerable, and growing, body of government controls. Necessary in the interest of public safety, such controls, add to the operating costs of the drug companies.

The Canadian drug industry cannot be considered in isolation, for this is among the most international of industries. Firstly, most of the major companies involved in providing Canadians with drugs of quality, like the research through which these drugs have been discovered, are international in scope. Research conducted in Canada both benefits from and contributes to world knowledge. Secondly, the conduct of business in Canada is very similar to that practised in other countries, subject to the specific requirements of government.

Another major factor bearing on our situation is that, as we know it today, this is a young, evolving industry. Essentially, the present pharmaceutical market has been created by the research discoveries of the past 30 years. In many fields, drugs which provide definite cures instead of alleviation of symptoms alone have become widely available. In addition, pain and suffering can be effectively treated in illnesses where no means of alleviation previously existed.

This has led to tremendous expansion of the industry in Canada as elsewhere in the world. Very many new products have been introduced, and there have been frequent changes in company leadership in the various therapeutic categories.

The Benefits Resulting from Research

The beneficial flow of drugs has at its source an intense, sustained effort in basic and applied research, based on international cooperation

between universities, hospitals, government and industry. However, it is the function of industry to turn the discoveries of research into drug products of therapeutic value. The Royal Commission on Health Services described the results in the following word:

> "The outstanding progress made in medicine in the present generation would not have been possible had it not been accompanied by major advances, and in some cases by a breakthrough in the discovery of new drugs and the development of improved pharmaceuticals to help physicians to combat and in many instances prevent disease and illness.
>
> "Effective and judicious use of drugs have made it possible not only to improve the health of the nation but also to raise the economic benefits resulting from the provision of health services.....
>
> "Advances in drug therapy in the last two decades have been particularly spectacular. Most of the progress made has taken place in such industrially advanced countries as the United States and the United Kingdom. Canadians have shared in this progress. The dynamics of progress in the drug field are illustrated by estimates which indicate that 90 per cent of the drugs prescribed in 1960 were introduced in the previous two decades; 40 per cent could not have been prescribed in 1954."
>
> (Report p. 340)

This lesson will be of only academic significance unless it influences the policies which shape the future. Very great challenges to medical and pharmaceutical research remain; they will not be overcome without the massive dedication of all resources. The major drug companies, for instance, are continually increasing their investment in research and development, even though this is yielding fewer new products. Although the cost of research is only one element in the total cost of prescription drugs, it is an important one. Further, only companies operating at a risk-related profit can afford the commitment to an uncertain future which maintenance of a large pharmaceutical research establishment demands.

The economic and social benefits of pharmaceuticals have been widely attested—for instance, through the control of formerly often fatal diseases such as diphtheria, pneumonia, tuberculosis and syphilis.

Most significant, too, are the savings to the community which arise from the use of drugs to combat mental illness. For instance, the rise in the admission rate to mental hospitals in recent years has been far exceeded by the rise in the rate of discharge, due in large measure to the availability of new medication. As a result, mental hospital residency per 100,000 population has declined steadily. According to the Dominion Bureau of Statistics, it dropped from 406.4 in 1955 to 352 in 1962. This has allowed major savings in the provision and maintenance of hospital beds.

On pages 426-9 of the Hall Commission report are printed tables giving the national expenditure on personal health services. From 1945 to 1961, prescription drugs varied from 6.2 to 7.9 per cent of the total expenditure—less than a third of the cost of physicians' services or a sixth of the cost of hospital services. (The figures for prescription drugs do not include drugs dispensed in hospital, but these come to less than a tenth of total hospital expenditures.) When all prescription drug costs are added together, they appear to amount to about 10 per cent of all health service expenditures.

In assessing the contribution prescription drugs have made to the national economy, a number of factors must be taken into account—for instance, the saving in productive time for millions of Canadians, who otherwise would not be able to work or take care of

their families, and the saving in the occupation of hospital beds and in the attention required from professional staffs. The present health care structure is, in fact, built on the ready availability of reliable pharmaceuticals.

The cost and value of prescription drugs cannot be properly assessed out of the total health care context. The national interest requires clear thinking about the impact of any price-oriented projects affecting drug availability on the adequacy of other health services, as well as about the ultimate cost to the country.

Relations with Government

It seems appropriate at this point to set out what we believe to be a workable philosophy of government-industry relations. Responsible citizenship demands wholehearted cooperation with those administering the laws of the country. In this spirit, our scientists and technical people have collaborated with the Food and Drug Directorate in the elaboration of many regulations bearing on standards for both manufacturers and particular products. We have consistently supported the strengthening of the Directorate, and put forward the concept of registration to assist the Directorate in enforcing its standards. Representatives of our Association serve on the Drug Advisory Committee, appointed by the Minister of National Health and Welfare.

Nevertheless, as a competitive industry in a free enterprise economy — and in an advanced industrial nation — we are concerned to protect what we believe to be the freedoms essential to our efficient operation. To serve the people of Canada properly, we must be able to conduct

our business realistically, and to make a fair profit.

A sense of practicality should determine the allocation of responsibilities to agencies of government. They have important regulatory functions. They can also assist greatly in obtaining and disseminating scientific and technical information. However, it is most undesirable that government become the final arbiter of therapeutic efficiency, or infringe upon the physician's professional rights and responsibilities.

BREAKDOWN OF THE PRESCRIPTION DOLLAR

This presentation is concerned with the various elements in the cost of prescription drugs which come within the control of the manufacturer. In general, as the table below shows, these amount to 37½ cents out of the prescription drug dollar. The remaining 62½ cents are required to ensure distribution through the retailer and wholesaler, and to pay the Federal sales tax.

The Canadian Pharmaceutical Journal of June 1965 carried the results of a national survey of prescription prices sponsored by the Canadian Pharmaceutical Association. This was conducted during two weeks of November 1964 by Professor H.J. Fuller of the Faculty of Pharmacy of the University of Toronto, and covered 223,000 prescriptions. It gave the average price of a prescription as $3.47, and the cost of the ingredients to the pharmacist as $1.73. When additional allowances are made for wholesale distribution and federal sales tax the manufacturer's portion of the average prescription is $1.30 or 37½ cents of the average prescription dollar.

The 37½ cents received by the manufacturer breaks down as follows (based on the PMAC annual statistical survey, Appendix E):

MANUFACTURER'S PORTION OF PRESCRIPTION DOLLAR

Manufacturing			11½ cents
Materials		8½ cents	
Labour		1½ cents	
Plant Costs		1½ cents	
Distributing and Warehousing Costs			1½ cents
Professional Service Representation, Marketing, and Medical Information			11 cents
Field Sales Expense		5½ cents	
Administration of Marketing, Selling & Advertising Functions		1½ cents	
Advertising & Promotion		4 cents	
Medical and Pharmaceutical Advertising	1 cent		
Direct Mail Advertising	1 cent		
Samples	1 cent		
Medical Exhibits, Space & Other	1 cent		
Research & Development			2½ cents
Royalties			1 cent
Manufacturing Administration			4 cents
Income Taxes			3 cents
Earnings			3 cents
	TOTAL		37½ cents

To express the same data in terms of the manufacturer's dollar, the breakdown would be as follows:

BREAKDOWN OF MANUFACTURERS' DOLLAR

	%	%
Manufacturing		30.0
Materials	22.0	
Labour	4.0	
Plant Costs	4.0	
Distributing and Warehousing Costs		4.0
Professional Service Representation, Marketing, and Medical Information		30.0
Field Sales Expense	15.0	
Administration of Marketing, Selling & Advertising Functions	4.0	
Advertising & Promotion	11.0	

	%
Medical & Pharmaceutical Advertising	2.0
Direct Mail Advertising	3.0
Samples	4.0
Medical Exhibits, Space & Other	2.0

Research & Development	7.0
Royalties	3.0
Manufacturing Administration	11.0
Income Taxes	7.5
Earnings	7.5
TOTAL	100.0

THE ECONOMIC STRUCTURE OF THE PHARMACEUTICAL INDUSTRY

The report of the Restrictive Trade Practices Commission contained quite detailed statistics about the pharmaceutical industry. These were reviewed and in part reproduced by the Royal Commission on Health Services. We will not, therefore, recreate this total picture, but rather comment on certain salient aspects, presenting our views in particular about those aspects which have become a matter of public debate.

Attached to this presentation as Appendix E are results from the latest annual statistical survey taken by the Association. It covers operations during 1964.

For the 41 reporting companies in 1964, sales of packaged human pharmaceuticals amounted to $110,465,396, not including proprietary or patent medicines. It is estimated that total sales of packaged human pharmaceuticals of all PMAC members amounted to $136,000,000. Of this amount approximately 70 per cent was distributed through retail pharmacies.

It should also be borne in mind that only part of the retail expenditure on human pharmaceuticals results directly from a doctor's prescription. Most of our products are bought only on prescription. Others, though frequently prescribed, may be bought without a prescription.

The Extent of Competition

Market surveys show that no single company holds as much as 6 per

cent of the Canadian pharmaceutical market. It is significant that in the three largest classes – antibiotics, hormones, vitamins and nutrients – no single company has as much as 21 per cent of the market, and that only in five of the 24 therapeutic classes into which the market is divided does the share of the top company exceed 40 per cent.

Writing in the Spring 1963 issue of the Patent, Trademark, Copyright Journal of Research, Education, George E. Frost, a noted patent attorney, brought out some significant facts about pharmaceutical industry competition.

> "The drug industry may be divided into a variety of product categories, the products within each category being directed to generally the same objectives and being in substantial competition with each other. The typical record for any particular product category is one of constant churning in so-called 'dynamic' competition – with dramatic shifts in market positions as existing drugs are displaced by superior products of rival houses. In cardiovascular preparations, the leading company in 1951 enjoyed about 19 per cent of the market, the leading company in 1960 had about 21 per cent of the market, and of the four leading concerns in 1951 only one was among the four leading concerns in 1960. In the case of diuretics, four different concerns enjoyed the leading market position in the 1951-1960 period, the concern with the largest sales in 1960 was not among those with significant sales in 1951, and the concerns with the largest sales in 1951, 1952 and 1953 had no significant sales in 1960. And in corticosteroids, the company that pioneered the field in 1950 had only about a quarter of the business in 1954 and by 1956 its products enjoyed less than 5 per cent of the market."

Extent of Manufacturing

Our brief to the Hall Commission, submitted in May 1962, reported that approximately 83 per cent of prescription products sold in Canada were manufactured here, the remaining 17 per cent being imported.

The term 'manufacturing' is used to describe the production of a pharmaceutical from its therapeutically active substance or substances. The processes involved are product development, formulation, mixing, compounding, tabletting, etc.

There are various reasons why it has not proved economically feasible to develop a pharmaceutical chemical industry in line with the pharmaceutical industry, itself. The first of these is the limited size of the Canadian market. According to DBS "Imports by Commodities," the total value of pharmaceutical chemical imports by manufacturers in 1963 came to about $20,000,000. This total was made up of a large number of separate products, few of which are required in any substantial volume. Further, the present tariff structure does not encourage the production of these chemicals in Canada.

In addition, where pharmaceutical chemicals are concerned, Section 67 of the Patent Act, which generally fosters manufacturing in Canada is over-ridden by Section 41. Evidence of manufacturing in Canada has not so far been considered a valid defence against a compulsory licence application made under this section.

Pharmaceutical companies in Canada have developed primarily to serve the domestic market, and at present, few of them are exportive. Certainly, it would encourage exporting activity if conditions in Canada fostered a more comprehensive manufacturing operation, including the manufacture of the active ingredients.

Employment and Purchasing in Canada

The pharmaceutical industry, which has expanded steadily in recent years, makes an appreciable and growing contribution to the national economy. Our 38 reporting companies had 6,098 employees in 1964,and total employment is estimated at something over 10,000. It is interesting to note that of the total employees of those companies reporting, approximately 25 per cent are university graduates.

Companies are substantial purchasers of goods and services in Canada. In 1964, out of a reported final sales volume of $107,790,000, materials purchased abroad and other payments accounted for about $22,215,000, the remaining $85,575,000 being represented by payments and investments made in Canada.

The total is made up as follows: (Appendix E, page 3)

Wages, salaries, benefits	$ 29,059,000
Materials employed in production	14,786,000
Excise, and income taxes	7,320,000
Depreciation and retained earnings	7,381,000
Other administrative, production and marketing services bought in Canada	27,029,000
	$ 85,575,000

The national value of the industry must be judged primarily on its fulfilment of its basic purpose: to make available throughout Canada pharmaceutical products of the highest quality, the fruit of the latest international research, at prices consistent with Canadian business costs.

Profits in the Pharmaceutical Industry

Profits in the pharmaceutical industry are consistent with the risks involved. This is a research-based industry in which progress results from vigorous and sustained competition. Companies must maintain substantial expenditures on research, both in Canada and internationally,

without any guarantee that specific projects will yield results even after years of investigation and development. On this depends the continuing availability of new and better drugs.

According to a review of profit ratios for 62 industrial classifications in 1962, published by the Canadian Manufacturers Association, profit as a percentage of sales for all manufacturing before taxes came to 7.6 per cent; this included several chronically or temporarily depressed industries. Pharmaceutical preparations were listed as 11.4 per cent. Manufacturing industries earning higher profits were: soft drinks; alcoholic beverages; pulp and paper mills; engraving; stereotyping and allied industries; office and store machinery; fertilizers and industrial chemicals. Total operating earnings before taxes reported by the 41 companies replying to our 1964 survey was 10.8 per cent on sales. The profit after taxes amounted to 5.2 per cent.

Return on sales is one indication of the profitability on an industry, but it is an unsatisfactory indicator of economic effectiveness because it fails to relate earnings to the resources employed. When the flow of earnings is so related for 1964 by our 41 reporting companies, the rate of return for the industry amounts to 15.6 per cent before taxes and 7.6 per cent after taxes. This would seem to be in line with results for other industries.

If, as the Royal Commission on Health services implied, fees for management services, royalties on patents, and dividends amounting to $5.77 million for 1964 to parent companies should all be included in the profit column, it would raise the rate of return on resources employed only 2.1 per cent

to a total of 9.7 per cent. But fees for management and royalties for use of patents are in no sense profits; they are a vitally necessary part of the cost of doing business; and were the Canadian companies obliged to obtain these services and pay the costs to other than parent companies, the total cost of operations could well be a great deal higher.

Research has been one area where pharmaceutical manufacturers located in Canada have been singled out by the Hall Commission. Its report questioned the value of the reported earnings of the Canadian drug industry because subsidiaries are being charged for research done by parent companies. We would like to state that although 37 of our members which answered a question on this subject reported that they spent in 1964, 5.5 million in research in Canada and were charged 1.5 million by their parent companies for research done in their behalf, our members have at their disposal the results of over $400,000,000 spent in research by the total world pharmaceutical industry.

Volume and Rate of Investment

The following figures summarize the volume and rate of investment for the members responding to the PMAC investment surveys for the years 1960 through 1964:

	1960	1961	1962	1963	1964	Total
No. of companies reporting	40	37	38	45	45	-
	($000's)	($000's)	($000's)	($000's)	($000's)	($000's)
Plant, January 1st	$46,775	$49,893	$53,177	$54,489	$57,747	
Additions, at cost	2,987	4,373	3,606	6,257	7,492	$24,715
Plant, December 31st	$49,762	$54,266	$56,783	$60,746	$65,239	-
Less: Dep'n in year	19,659	20,268	21,915	23,767	28,034	
Plant, Dec. 31 (Net Book Value)	$30,103	$33,998	$34,868	$36,979	$37,205	$24,715
Depreciation charged during year	$ 2,157	$ 2,300	$ 2,404	$ 3,046	$ 2,881	$12,788
Equity investment (including retained earnings)	601	3,865	3,079	6,349	8,834	22,728
	$ 2,758	$ 6,165	$ 5,483	$ 9,395	$11,715	$35,516

As these figures show, the investment of PMAC members responding to the survey was $65,239,000 at gross book cost at the end of 1964 and $37,205,000 at net book value. Thus, gross investment increased by 39.5 per cent from January 1, 1960 to December 31, 1964, or a simple annual rate of 7.9 per cent. If anything, these figures understate the normal rate of investment, as the years 1960-1962 inclusive were relatively depressed and were not, therefore, conducive to a high rate of investment. Additions to plant in these years as a percentage of plant at gross book cost at the beginning of each year were as follows: 1960, 6.4 per cent; 1961, 8.8 per cent and 1962, 6.8 per cent. The years 1963 and 1964 were more prosperous and resulted in a rate of investment of 11.5 per cent and 13 per cent respectively of the gross investment in plant at the beginning of each year. The average annual rate of investment on this basis over the five-year period was 9.3 per cent.

It can be seen from the data that depreciation charges were just over one-

half the total investment in plant during the period and that, in every year, plant investment exceeded the depreciation charged during the year. The balance of funds needed for plant investment came from retained earnings and other long-term capital from ownership sources.

Investment in inventories actually increased by $8,625,000 over the period. When this is allowed for, the total investment in plant and inventories, totalling $33,340,000 over the five-year period, was closely balanced by depreciation charges, earnings retained in Canada, and new funds. The difference of $2,200,000 helped to finance the increase in Accounts Receivable and other assets associated with rising sales that was not provided for by trade credit and other forms of debt capital.

Another test of the economic effectiveness of an industry is that the role of investment be commensurate with the rate of earnings of the industry. In this respect the pharmaceutical manufacturing industry meets the test of good corporate citizenship because, not only are all retained earnings and depreciation funds plowed back into the business, but a new flow of fresh capital is provided by additional direct investment.

Tax Payments

The members of our Association responding to the annual surveys report that over the five-year period from 1960 - 1964, inclusive, they paid excise and sales taxes of $43,783,000 and income taxes of $41,712,000. Their net income over the period totalled $43,781,000, of which $21,053,000 were paid in dividends. Two interesting relationships are disclosed by these figures: for every dollar earned, the companies paid two dollars

in taxes; and for every dollar paid in dividends, the companies paid four dollars in taxes.

THE COST OF DRUGS TO CANADIANS

It has been widely maintained that the cost of drugs to the Canadian consumer is unduly high in comparison with what is paid in other countries. Notably, the "Green Book" of the Director of Investigation and Research, published in 1961, contained a number of international comparisons, based on evidence produced before the Kefauver Committee (pp. 203 - 217). These comparisons were made in terms of actual prices, translating the foreign currencies into Canadian dollars. They did not take into account either standards of living or earning powers in the countries concerned.

To present a fair picture of the cost of drugs to Canadians, it is, we believe, essential that these factors be related to the prices paid.

In order to present such a picture, we selected 17 drugs selling in good volume under their brand names in Canada. The selection was made according to the following criteria:

1) They represent a broad view of the most important therapeutic classes;

2) They are the products of a number of major drug companies;

3) The same products are sold in similar strengths and dosage forms in other countries.

The products used were:

Achromycin	Librium	Peritrate
Chloromycetin	Equanil	Doriden
Terramycin	Stelazine	Seconal
Penbritin	Ismelin	Pyribenzamin
Gantrisin	Hydrodiuril	Banthine
Decadron	Diuril	

We selected the following countries for comparison with Canada: United States;

United Kingdom; Italy; West Germany; France; Holland, and Sweden. We obtained details of the drug prices in these countries, and translated them, where necessary, into Canadian package sizes.

Wage rates of manufacturing employees in seven of these countries for 1964 were obtained from the Yearbook of Labour Statistics (I.L.O.), 1964 (p. 345 et seq.) and from the "Monthly Bulletin of Statistics," (United Nations) July 1965, (p. 128, Table 57). Wage rates of manufacturing employees in the United Kingdom were derived from the Yearbook of Labour Statistics (I.L.O.) 1964 (p. 362, Table 16) and the Ministry of Labour Gazette (London), January 1965, H.M. Stationery Office, Volume LXXIII, No. 1, "Rates of Wages and Hours of Work, in 1964," p.9. The following figures were used:

Country	Hourly rate in manufacturing	In Canadian dollars
Canada	$2.02	$2.02
U.S.	$(US) 2.53	$2.72
U.K.	6/11½d	$1.04
West Germany	M.3.73	$1.01
Italy	Lire 373	$ .64
France	Francs 2.86	$ .63
Holland	Guilders 2.38	$ .71
Sweden	Kroner 7.12	$1.49

We then related these wage rates to the selected drugs, and obtained comparisons of drug prices in terms of labour hours. The comparisons were worked out both for actual hours of labour and as an index of labour hours, using Canada as 100. (These comparisons and the prices used both in domestic currencies and in Canadian dollars are attached as Appendix F.) It should be borne in mind that the Canadian prices include the impact of the Federal sales tax, increasing the price to retailer by approximately

10 per cent, and the price to consumer in similar proportion.

Finally, a simple average was developed for the hours of labour indices, and this shows in general terms the relationship of Canadian drug prices to those of the other countries:

Country	Indices of Price to Retailer
U.S.	79.15
Canada	100.00
Sweden	104.31
U.K.	129.40
West Germany	168.88
France	235.08
Holland	237.46
Italy	243.00

The most significant finding is surely that most products cost less in terms of labour as the standard of living rises, and Canadians therefore can buy their drugs with less labour than people in most other countries. It is also significant that, despite the existence of a National Health Service in the United Kingdom, the real cost of drugs there is still appreciably higher than in Canada. In Sweden, a country where the standard of living is approximately the same as in Canada, the price to the retailer is in line with the Canadian price.

DISTRIBUTION AND PRICING

Methods of Distribution

A pharmaceutical manufacturer may distribute his products in various ways. To hospitals and governments he will normally sell direct, though hospitals on occasion buy through the regular trade channels. Products for retail sales are either sold direct to the pharmacist or go first to a wholesaler. This also holds true for dispensing doctors.

Many larger companies prefer to sell direct to the pharmacist. They maintain warehouses or depots in strategically located cities such as Moncton, Halifax, Montreal, Toronto, Winnipeg, Calgary, Edmonton and Vancouver. In some cases, manufacturers own or operate their own warehouses; in others, a number of manufacturers use the facilities of a warehousing company.

Certain companies distribute entirely through wholesalers. They include some larger companies and most of the smaller ones, which would not find it economical to maintain their own distribution facilities.

To ensure that drugs are available in retail and hospital pharmacies immediately or with a minimum delay requires a nationwide network of wholesalers, carrying substantial stocks. In this country, with the population scattered over such an immense territory, servicing all drug outlets constitutes a tremendous distribution problem.

Individual companies choose the distribution system which will be most economical in view of the size and nature of their market. None, however, relies entirely on its own facilities; all use wholesalers to a certain degree.

Pricing Considerations

Many factors must be taken into account when pricing a prescription drug, most of them related to the particular market for which the product is destined.

The likely sales pattern has to be forecast. This will be determined by the size and nature of the market, the competitive strength of existing products, and the specific therapeutic advantages offered by the newcomer.

The type of therapy for which the drug will be mainly used is also significant. If it is likely to be taken over a long period, pricing will be worked out in terms of the daily cost of therapy. For other products the total cost of therapy, based on the anticipated size of the average prescription, will be the key consideration.

There are certain operating costs which the sales of all products must cover if they are to be commercially successful. (Some products of value in treating rare diseases or conditions are consciously sold at a loss, or provided at no charge.)

There must be a proper allocation to the company's research program. This cannot be an attempt to recover the cost of the research behind a particular product, for that can be estimated only in quite general terms; each success is built on many failures. Rather, the new product must make a reasonable contribution to the ongoing research activity of the company, an activity which is becoming increasingly expensive.

The cost of production, estimated on the basis of the expected sales

volume, must be covered. This includes the cost of ingredients, labour, quality control, and a proper allocation of plant overheads. Then there are the general administrative costs.

There is also the cost of an effective program of information and promotion. The various elements of such a program and the related requirements of an adequate information service and a successful marketing effort are discussed in the section entitled "The Cost of Marketing" (Section 9). Significantly, the early years of a product are those in which marketing expenditure is heaviest; without such expenditure medical awareness and use of the product can be delayed for a very long time or even indefinitely.

Finally, there is the cost involved in the manufacturer's policy of returned goods, which we believe is unique in the manufacturing industry in Canada.

The ultimate pricing pattern will be determined to a varying degree by all these factors.

The Pricing Structure

It has been a policy of the Association to refrain from any activity in the matter of price and the pricing practices of its members.

Our member companies must unilaterally determine their own policy in this area. Until the enactment of Section 34 of the Combines Act, most companies established the resale price. Since the enactment of this section, it has been a common practice in many manufacturing industries to suggest a retail price. Most pharmaceutical manufacturers

have continued the practice of selling to retail pharmacists at a discount of 40 per cent off this price.

However, some manufacturers have given up this system for "prescription only products" and have adopted a policy of quoting "net" prices to pharmacies.

In contrast to the retail market, there is no clear pricing pattern known to us for drug purchases by hospitals, institutions and government. Prices here are influenced by a number of special considerations and also depend upon the individual manufacturer's policy.

The Reasons for Multiple Pricing

Differences between the price to the retail pharmacist and the price to hospital or government have been documented by the Director of Investigation and Research under the Combines Investigation Act in the "Green Book." In some cases the difference was substantial. The industry may reasonably be asked to explain why such differences occur.

Various causes may be involved. Firstly, hospitals do not pay the 11 per cent sales tax. Secondly, these customers buy in large quantities, and the offering of discounts to bulk purchasers is a normal business practice, justified by the savings in operating costs.

In addition, other considerations can carry weight, depending on the nature of the product. It may be advantageous to the manufacturer to have his product used substantially in hospitals, so that physicians become acquainted with it, and are therefore more likely to prescribe it in their own practice.

The competitive situation will have a strong influence. There is continual competition within all therapeutic categories. However, when the competition comes from a so-called generic equivalent, the original manufacturer has to decide whether to abandon the hospital or government market, or to reduce his price to a level which will meet that of a company which has not faced the costs of either research or product introduction, and carries little or no scientific overhead. In effect, he is forced to compete for business, often based on quite general specifications, against naturally cheaper, and it may well be, inferior, products. He will do this to maintain an important market or to protect the reputation of his product; in the event of the failure of a so-called equivalent formulation doctors may well blame the drug itself.

THE COST OF MANUFACTURING AND QUALITY CONTROL

Our 1964 statistical survey (Appendix E) shows that the manufacturing cost of goods for human pharmaceuticals is estimated at 32 per cent of net sales.

Within this total there is an allocation for quality control— the maintenance of a quality control laboratory, or payment for laboratory services, combined with the many special services in the production area required to meet the proper standards of prescription drug manufacturing. To measure the real extent of these expenses, we asked our members to reply to a detailed questionnaire. This was based for the sake of convenience on the similar standards which have been developed by the Canadian Government Specifications Board. (Representatives of our Association worked with government in drawing up these standards, and a number of companies helped to train the inspectors who apply them.) The results of this questionnaire are attached as Appendix G. They show that the various activities related to the assurance of pharmaceutical quality account for about 10 per cent of manufacturing costs.

However, effective quality control must take into account a company's entire operations through a series of interlocking controls.

The Committee is again referred to the Associations previous submission, June 19, 1964.

THE COST AND VALUE OF RESEARCH

To assess the value of pharmaceutical research in relation to its cost requires the awareness of certain basic facts. First, a company must maintain its research activity at an increasing cost even though there is no guarantee of success or profitable return. In electronics, for instance, once the problem is posed a research answer can be expected; this is not the case with mankind's reply to the challenge of disease. International expenditures on pharmaceutical research now exceed $400,000,000 a year, and individual companies can, and do, spend millions of dollars on specific projects--sometimes successfully, and sometimes with no result at all apart from the knowledge of what cannot be accomplished. It is estimated that only one in every 3,000 compounds tested will yield a drug of sufficient value to justify its introduction.

The Hinchliffe Committee report to the British Minister of Health states: "Really outstanding drugs are still very few in number and if a firm makes one major advance in 10 - 20 years it is doing very well" (p. 73). Research money, is, of course, expended in many areas and provides, too, its quota of less important advances. Yet these advances can themselves be vital aids to saving life and easing suffering. Exploiting initial break-throughs, they may provide effective medicines for related diseases, drugs with fewer side effects, more potent drugs or products that are easier to administer. Also, research will yield drugs of great value in so limited a therapeutic field that they are not commercially profitable. Yet the responsible

company will ensure that such products are widely available and physicians are fully informed about them.

The second basic fact of pharmaceutical research is that it is both a cooperative and a competitive endeavour. The industry is international in scope and activity, and nowhere more so than in its approach to research. Fostering the health of any nation requires that the fruits of world-wide research be made available to the medical profession as rapidly as assurance of safety will allow. No country, even the most advanced, can afford to restrict its physicians' armamentarium to products discovered by its own scientists. Similarly, every health scientist relies on the stimulation provided by progress in many countries.

There must also be frank cooperation among the various sources of new knowledge. This means a continuing exchange between university, hospital, government laboratory and pharmaceutical company. It would be extremely short-sighted to shut any one of these groups off from the others, or to limit its ability to communicate openly.

On the other hand, the pharmaceutical industry is intensely competitive, and in the past quarter of a century competitive enterprise has created and made available a tremendous range of life-saving and other essential drugs. Naturally, there is a certain waste; two or more companies will pursue the same objective, and products can be rendered obsolete almost as soon as they are marketed. But it is our strong contention that a research-based industry develops its potential to the maximum only under the spur of sustained competition. Government may well foster specific projects, but close direction of research will only inhibit

endeavour and place barriers across what is already a hard and demanding road.

In this connection, the patent laws perform a particularly valuable service, since to obtain a patent an inventor must reveal the facts of his invention. This information in turn suggests new goals to other researchers and steers them away from work that will result only in duplication. On the other hand, lack of patent protection leads to a disruptive secrecy as well as generally discouraging investment. Such a system of international research relationships, cooperative but also competitive, provides mankind's best hope for new life-saving medicines. The investigations now under way into both cause and cure are far-flung and intensive: cancer, heart disease, virus diseases, multiple sclerosis and other scourges are the immediate targets of pharmaceutical research scientists around the world.

The Need to Apply Knowledge

Basic or fundamental research can perhaps best be described as an investigation into the nature of materials and substances. Applied research, on the other hand, is concerned with the attempts to find practical applications for new basic-research findings. Appropriately enough, basic research is carried out in the universities while applied research is the province of industry. Man benefits from the fruits of important new knowledge only as industry can devise the means to make it available, at the same time often widening the scope of the benefits far beyond the initial concept of the inventor. Further, the pure research may well have been sponsored or aided by industry, as for instance, in the discovery of streptomycin by Dr. S. Waksman

and much of the pioneering work that led to cortisone.

The story of penicillin highlights these principles. In 1928, Sir Alexander Fleming sought help to develop his discovery, but was unsuccessful. After thirteen years the interest in penicillin revived and the pharmaceutical industry, supported financially by government to meet the needs of wartime, developed mass production processes. Subsequently, industry, itself, has added enormously to man's knowledge of penicillin therapy, greatly reduced the cost of production, and discovered several new and more effective varieties of the drug.

Today, companies spend millions of dollars exploring areas of knowledge which may, or may not, yield marketable products. They can do this only if their revenues from existing products encourage such activity; a research-based industry, where there is strong competition in product improvement, is inevitably a high-risk industry.

The Sequence of Research

Basically, the aim of pharmaceutical research is the discovery and synthesis of new chemical compounds, followed by their testing for beneficial biological activity and their final translation into safe and effective products. Each new and potentially therapeutic substance presents its own problems and requires specialized treatment, but the following are the main steps in research and development:

1. Synthesis of a new compound (or the discovery and identification of compounds currently existing in nature):

These require fully equipped and staffed chemical laboratories.

2. Pharmacological testing: The biological activity of chemical compounds can be assessed only in animals — in vivo, not in vitro. Any new compound must be screened through numerous costly and time-consuming tests.

3. Toxicity: Once effectiveness has been established, undesirable side effects and toxicity must be evaluated in the same way. No human trials can be permitted until there has been extensive toxicological evaluation.

4. Dosage form: Dosage forms must be designed to provide the active ingredient of the product in its most therapeutically effective manner.

5. Initial Clinical Trials: Before a new substance can be used in clinical trials, permission must be received from the Food and Drug Directorate. Toxicology and manufacturing procedures in addition to the animal pharmacology must be submitted.

   Once the substance passes these tests, a period of cautious evaluation in humans can be undertaken under stringent supervision of the manufacturer and the government.

6. Further testing and clinical trials: Should the promise of the drug be reinforced by these first trials, the compound is subjected to a new round of intensive pharmacological and toxicological evaluations. At the same time it is tested in more extensive clinical trials.

7. New Drug Submission: All the evidence gathered through these various stages is presented to the regulatory authority. In Canada, a "notice of compliance," issued by the Food and Drug Directorate, is required

before the product can be marketed.

These activities were reviewed in greater detail in our presentation on drug safety to this Committee. (Minutes of Proceedings and Evidence No.7). The related administrative procedures are laid out schematically in Appendix H of this submission.

Research on the biological properties of a drug cannot stop with its introduction. Some of its actions, both useful and undesirable, may become apparent only when it has been used extensively in medical practice. Such actions will require further evaluation and laboratory work. In addition, physicians' experience may point to ways in which the product, itself, can be improved. The originating, research-based company will devote considerable resources to this activity and make strong efforts to receive continuing clinical reports on the action of the drug.

Clinical Research in Canada

Most of our member companies maintain an active program of clinical research in this country which is essential to confirm the safety and efficacy of a drug before the drug is marketed, and which complements other clinical research performed in other countries.

This activity has stimulated the development of clinical research facilities in Canada, and, in addition, members of the PMAC financed in 1963 the establishment of the Canadian Foundation for the Advancement of Therapeutics. Dr. F.S. Brien, Head of the Department of Medicine at the University of Western Ontario, accepted the chairmanship of the Foundation.

To date, the Foundation has financed nine fellowships and eight studentships as well as several research projects. A three-day symposium on

human pharmacology, bringing together Canadian and American leaders in the field, was organized in the fall of 1964. About one hundred representatives of the universities, government and industry attended. The theme of the conference was the improvement of drug evaluation in Canada, and another conference is projected for this year.

The Foundation is the foremost organization in Canada devoted to the support and development of clinical pharmacology.

The Cost of Research

The expenditure required to bring a new drug to the market has been increasing sharply. The Pharmaceutical Manufacturers Association of the United States estimates that the average cost of the research behind a new drug is now $5,000,000, compared to $2,700,000 five years ago. Factors accounting for this are: the general increase in research expenses; the growing complexity of much pharmaceutical research both chemical and biological; a shift in emphasis from the treatment of symptoms to the treatment of chronic diseases. In addition, far more extensive requirements of regulatory authorities call for expensive and prolonged testing in animals which must be carried out before the drug is ever given to a human.

The accumulated data needed to satisfy Food and Drug Directorate requirements before a new pharmaceutical may be made available for limited human clinical investigation often forms a stack of documents several feet high. (See Exhibit A).

Both in Canada and the United States, the requirements of government

for additional data before a new drug is allowed on the market have sharply increased companies' R&D expenditures. Chemical and Engineering News, the organ of the American Chemical Society, in a special report on the pharmaceutical industry (August 10, 1964) stated:

> "Industry research people estimate that the cost of developing a new chemical entity has increased somewhere between 20% and 50% in the past few years, with most of the increase due to meeting the requirements of FDA."

There is general agreement that the cost of research in all fields is rising. Dr. L.R. Thiesmayer, President of the Pulp and Paper Research Institute of Canada, in a paper prepared in June 1964, estimated that in Canada as in the United States, it costs from 5 to 7 per cent more a year "just to stand still in research."

The rate of discovery in any research-based industry fluctuates, and the past few years have witnessed a marked reduction in pharmaceutical research productivity, as reflected in the introduction of new chemical entities. In the United States, from 1954 to 1961 the annual rate ranged from 31 to 63 new products. It dropped to 27 in 1962, 16 in 1963 and 17 in 1964. However, in 1965 the number of introductions rose to 24, due in part to more rapid processing by the regulatory authorities. A similar pattern can be discerned in new product introduction in Canada.

New Avenues of Research

The Wall Street Journal of November 9, 1965, in a review of new drug developments, quoted Charles S. Brown, Executive Vice-President of Abbott Laboratories as follows:

> "While we still look for better drugs in areas where we have attained success, as in antibiotic therapy, our major interest lies in drugs of the future that will fight cancer, viral and parasitic diseases, and cardiovascular and other degenerative ailments."

This statement was amplified by George S. Cain, Chairman and President of Abbott Laboratories:

> "Current efforts are pushing us deeper into the incredibly complex machinery of the cells, tissues, and organs of the body. We are trying to unlock the roles of nucleic acids, enzymes and amino acids in life processes and looking into the maze of the body's defence mechanisms."

Such research is, in fact, an excellent example of the way that pharmaceutical companies apply the original concepts of the university scientists.

Expenditure in Canada

Expenditure on research and development in terms of net sales in the pharmaceutical industry runs at about three times the average for manufacturing industry in general. Information relating to this expenditure in Canada was provided by our member companies as part of the 1964 statistical survey (Appendix E.)

The Hall Commission is critical of the expenditure on research by Canadian companies on two counts: the amount spent in this country and the amount charged for work done elsewhere. (p. 667 and p. 678). With regard to the former, it is significant that, whereas in 1959 companies reported research expenditures of $2,500,000 in Canada, by 1965 this sum had risen to $6,500,000. There has been a steady expansion of pharmaceutical research in this country--clinical investigation and also laboratory activities. Should conditions remain favourable to such research, there is every indication that the present rate of growth will be well maintained in the years ahead.

The origin of the misunderstanding that gave rise to the second criticism is explained in Section 3 of this brief.

A Choice for Canada

Pharmaceutical firms are increasing their research investment in Canada, but it would be unrealistic to claim that we can ever be the authors of a major proportion of the prescription drugs used in this country. We can be worthy collaborators in an international venture, but this must remain an international industry, with the main foci on endeavour in those countries where the major companies have been long established.

The Expansion of Canadian Research

The members of our association are keenly aware of the factors favouring research activity in this country—notably, the availability of scientific and technical people of high calibre, and the relationships possible with a number of outstanding universities. They have responded to these advantages, and to the fiscal and other encouragements offered by government, with a marked increase in both investment and annual expenditures since their introduction in 1961. Our research facilities have been greatly expanded since the Hall Commission report was documented.

Nine of our members now operate research and development laboratories in Canada. Further growth can certainly be expected so long as the treatment of our industry does not preclude the necessary investment.

Scientific personnel employed by the industry on research and development work have increased substantially in recent years. For instance, the number of physicians employed full-time in research by members of

the Association rose from 12 in 1958 to 45 in 1964. At the last count—in 1964—there were 73 PH.D's or D.Sc's working in company research laboratories, 31 M.Sc's and 108 B.Sc's or B.Phm's.

This expansion of research activity in Canada reflects the growing scientific maturity of the country. However, it takes time for a new laboratory to become productive — as much as five to ten years from its establishment to the marketing of its first compound. And even the best staffed and equipped laboratories are of themselves no guarantee of success. Indeed, the uncertainty of success can be directly related to the significance of the potential benefits.

PUBLIC SERVICE PRODUCTS

As mentioned in the preceding section, the research laboratories of the international pharmaceutical companies have developed many products, often life-saving, that are specifics for rare illnesses and conditions. These products are often made available to physicians either free of charge or at factory cost. A recent survey of our members showed 18 companies listing 84 products of this type. The cost of these products cannot be easily determined but their value to Canadians is inestimable.

The products, themselves, fall into six categories.

1) There are drugs which are used to combat rare diseases and conditions. For instance, one company provides the sole or principal source of food indicated for infants and children suffering from phenylketonuria, an inborn error of metabolism which otherwise results in severe mental retardation. Another company provides free of charge for indigent patients its products that serve to control cerebral palsy and myasthenia gravis. A third company provides an antitoxin for botulism, a rare but often fatal type of food poisoning. A fourth distributes the product to combat pseudomonas (bacterial) infections in the eyes or bowels.

2) A company involved in anti-cancer research makes available to physicians certain pharmaceuticals that have proved themselves partially effective in the treatment of particular cancers, but have not justified a general introduction.

3) There are occasions when somebody in Canada suffers from a disease which is common elsewhere in the world but, happily, not in this country. Specifics are made available against leprosy, sleeping

sickness and malaria as well as sera against snake or black widow spider bite. A recent addition is a drug for the treatment of Schistosomiasis or Bilharzia.

4) Specialized forms of commercial products may be provided without charge when these are specifics for rare conditions, for instance an injectable form of a drug needed in an acute hypertensive crisis.

5) A number of companies provide the agents for specialized diagnostic procedures. These may relate to rare diseases such as trichinosis (swine fever) or brucellosis (undulant fever). Another example is the agent to diagnose toxoplasmosis, a rather unusual condition which results in the birth of a blind baby. The mother has no apparent symptoms, but the disease is known to be carried by dogs, and has on occasion reached epidemic proportions. Several agents are made available to physicians for the diagnosis of rare blood and renal conditions.

6) Products required in unusual surgical procedures may also be provided. One such product is essential to protect the cornea during a particularly intricate type of eye surgery.

THE COST OF MEDICAL INFORMATION AND MARKETING

In our introduction we stated that this presentation would endeavour to answer the question: "What are the reasons for the present level of drug prices in Canada?" Clearly, related questions of great importance are: "What do pharmaceutical companies spend on marketing?" and "Why do they need to spend so much?"

Marketing Expenses

Our Annual Statistical Survey for 1964 (Appendix E), presents the marketing expenses for 41 PMAC companies. Physicians' information, covering the provision of information and promotional material to physicians, accounts for 23.3 per cent of the manufacturer's sales dollar. Other Marketing Expenses, primarily direct selling to the pharmacist account for 6.6 per cent. The net result is that the manufacturer's marketing expenses amount to approximately 11 per cent of the prescription dollar.

The Requirements of Effective Marketing

To secure and maintain medical acceptance must be a major part of operating costs in this industry. Companies have to ensure that every physician and pharmacist across Canada is properly informed about their products; they are in business on a nation-wide scale. The fixed cost of the necessary marketing machinery must be borne whether or not a particular product is commercially successful.

Further, companies do not benefit from the savings provided by a mass market. They handle a large number of separate products, many of them

with quite limited sales volume. In fact, at present in Canada only nine prescription drug products have an annual manufacturer's sales revenue exceeding $2,000,000.

In their marketing, companies follow a pattern of activity common to most industrial countries. We do not believe that the justification for any significant deviation from this pattern within a free enterprise economy has been established for Canada.

Certainly, the managements of pharmaceutical companies are keenly aware of the cost of marketing their products. It can surely be assumed that as responsible men in profit-making enterprises they would not make the required resource commitment if they did not expect it to be productive. In fact, it is a condition of business survival.

The Impact of Geography

The geographical and other facts of doing business in Canada have to be faced. We are operating across a vast country with scattered population. Qualified representatives must be paid salaries on a North American scale. But except for those who serve in major cities, where there may be a concentration of physicians in a small area, they cannot hope to maintain a call-average comparable with other western countries. Territories are large, and travel expenses are high. And the current rate of detailing expense prevails even though companies find there are many sparsely populated areas where they cannot afford to send representatives. In this case, they have to rely on journal advertising and literature to carry essential information and promotional messages.

The Cost of Two Languages

The cost of providing full information and promotion services in two languages is also substantial. Practically all printed material is developed in both English and French versions. This calls for highly qualified translators and the duplication of relatively short printing runs. Companies estimate that their marketing expenditure is increased appreciably because of the need to do business in two languages.

The Balance Between Information and Promotion

In its marketing activities, a pharmaceutical company is concerned with two related requirements — the provision of scientific information and the promotion of its products. Theoretically, it would be desirable if a company could do business successfully through the single introductory provision of objective data about its products. Were the distribution of drugs in the hands of a monopoly concerned only with the sale of existing products, this might be feasible. But the success of this industry in developing useful new drugs and ensuring their wide availability is founded on competition and enterprise, including effective promotion. It has never been argued that the industry has failed in this, its most vital service.

Two characteristics largely fashion our marketing practices. On the one hand, drug products are numerous, varied and, increasingly, potent and complex. On the other, the use of those products is determined by the 20,000 members of the Canadian medical profession. In fact, when those who do not practise, or who have the kind of practice which involves drugs to only a minor degree, are eliminated, the determining group comes down

to about 15,000. The result is the direction of extensive information about a large number of products to a rather small number of professional people to whom the system seems acceptable and effective. (See Appendices I and J)

Marketing Standards

An established pharmaceutical company knows that its greatest asset is its reputation with the medical profession. This reputation is based on the reliability of both its products and the information it provides about them. Further, both are subject to control by the Food and Drug Directorate. The FDD not only passes judgment on safety and efficacy; it must also approve the basic circular about a new product on which all promotion is based, and has lately established in cooperation with the industry definite requirements and standards for advertising material. These have been incorporated by our Association in its own more extensive code of marketing practices (Appendix C).

An established company is not going to jeopardise its standing with the medical profession by wilful misrepresentation or exaggeration. There is too much at stake for the patient and his physician, as well as for the company itself. If there are side effects and contra-indications associated with a particular drug, the company will make sure these are properly presented. But at the same time a company is going to place before the doctor the advantages of its particular products.

The Purposes of Promotion

The first purpose of pharmaceutical promotion is to arouse interest in a new product. The product has demonstrated its therapeutic value —

otherwise it would not have obtained a notice of compliance from the Food and Drug Directorate —— but it is most unlikely to be the only effective medicine in a particular field. It will present definite advantages for patients with certain conditions. But it cannot come to be widely used unless physicians are properly informed about it.

The requirement is not merely commercial, but is directly related to the social responsibilities of the pharmaceutical industry. Delays in informing doctors about new drugs, once these have received a notice of compliance from the Food and Drug Directorate, can well cause unnecessary loss of life and suffering.

If we assume, as we must, that doctors have the education and experience to judge the value of the new product in their own practice, then company promotion is a means of assisting them to serve their patients. It is an Association policy to respect the wishes of the physicians with respect to his receipt of product information, either by direct mail or by professional representation. The doctor under our present system is a free, responsible professional; he can accept or refuse the products available to him. One of the standards by which his professional standing is judged is whether he does this wisely.

Pharmaceutical marketing activity—— information, promotion and advertising—— cannot be limited to new products. New information may become available about existing products, new indications may develop or new contra-indications. And companies have repeatedly found that the market for even well-established products depends on the maintenance of the

promotional flow—a fact of competitive enterprise in a dynamic industry. There is continuing enlargement of knowledge and shifting of preference, and each company must do its best to influence the patterns of use which emerge—within the limits set by scientific reliability and responsibility.

The Results of Pharmaceutical Marketing

It is important to visualize the total effect of the marketing and distribution operation. Today there are approximately 8,000 prescription preparations available in this country. This includes the various brands, formulations and dosage strengths, (Hall Commission Report, quoting Canadian Pharmaceutical Association, p. 347). These products are immediately, or very rapidly, available through any of the 5,000 pharmacies across the country, with the pharmacies stocking, themselves, all those for which there is a significant demand. All required drugs are equally available in all hospitals. At the same time, physicians, dentists and pharmacists are kept informed about these drugs—advantages, prescribing information, side effects, contra-indications—and new knowledge about them, once validated, is brought rapidly to their attention.

In these circumstances—the need both to be geared up for new product introduction and to maintain the flow of effective promotion—marketing becomes a rather rigid cost for a pharmaceutical company. The investment in good representatives and other marketing personnel must be protected just like the investment in good research workers. A company cannot hire and fire to match an irregular course of new product introduction.

Attached as Appendices D and I are more extensive reviews of the purposes and cost of detailing and pharmaceutical mail respectively, the major elements—together with journal advertising—of pharmaceutical marketing programs. The practice of sampling is discussed in Appendix J. How these various elements are combined is, of course, a decision for the individual company, influenced by the nature of its products and its past experience.

A Drug Information Service

One feature of the present system of drug information is that practising doctors receive most of their basic information about prescription drugs from the companies which manufacture them. While medical journals carry reports of clinical investigation and unusual cases, these will likely appear some time after a drug has come onto the market and be limited to particular aspects of therapy. Also, relevant articles will be scattered through many journals which the busy practitioner does not have the time to check and peruse.

The need has been recognized in Canada by doctors, pharmacists and manufacturers alike for objective, independent reporting on new products. The same need has been felt in the United States, where the American Medical Association has decided to set up a well-staffed service to provide information to its members through regular bulletins about new drugs and an annual publication collating its findings. At the initiative of our association, a committee has been set up to investigate the development of a related drug information system in this country. Represented on it, too, are the Food and Drug Directorate,

the Canadian Medical Association, the Canadian Pharmaceutical Association, and the Canadian Society of Hospital Pharmacists.

It is our strong opinion, coinciding, we believe, with that of the medical profession, that this is a task for an independent professional body, composed of representatives of medicine and pharmacy, operating with the support of government, not a responsibility of government, itself. There is, we believe, a marked danger of the views of an official body being treated as a seal of official approval or disapproval, and so becoming an undesirable limitation on the professional freedom of the physician.

What impact such a service would have on the cost of pharmaceutical promotion cannot be forecast accurately. If the profession should show by its prescribing patterns that reliance was placed on the service, companies would naturally revise their promotional programs to take account of such reaction.

Non-product Services

As noted in the survey reproduced as Appendix E, companies include in their marketing expense the cost of a number of activities which are not directly related to product information or promotion. Such activities have, of course, a general marketing purpose—establishment of the company in the minds of doctors as a responsible, scientifically-oriented organization. They provide valuable services to post-graduate medical and pharmaceutical education not available from other sources. Among these are: the organization of symposia relating to particular diseases; and distribution of the record of proceedings; and the support of professional meetings in various ways, including closed circuit coloured television

facilities, setting up of international telephone links, and the recording and distribution of proceedings.

THE COST OF SAFETY

The cost of safety pervades all sectors of our business; it is a growing cost, deriving from the awareness of government, industry and the medical profession of the toxic potential of modern pharmaceuticals.

Impact on Cost of Research

During the early years of the "wonder drugs" the exciting benefits of these newcomers tended to obscure the risks involved. Delays which companies now encounter in getting new products approved—whether for clinical testing or market introduction—have markedly increased research and development costs along the lines reported in Section 7.

The chart attached as Appendix H shows the current course in Canada of a new drug application, including the toxicological and clinical studies required, with their related paperwork.

Physicians on the staffs of member companies direct clinical research activity and provide an information service to practising colleagues, a service backed up by extensive scientific libraries, here and abroad. Much of their work relates to patient protection.

Impact on Cost of Manufacturing

Maintenance of responsible standards of quality control, referred to in Section 6 is another aspect of the expenditure on safety.

Impact on Cost of Marketing

Safety has also had its impact on marketing expense. As mentioned in Appendix J, the present sampling regulations, designed primarily for

reasons of safety, have increased the cost of sampling for most manufacturers.

So does responsible promotion in general, with its awareness of the need to ensure that full information about side effects and contra-indications is widely disseminated among physicians and pharmacists. To increase substantially the supply in Canada of imitative and inferior products handled by firms who do not share this attitude or the originator's intimate knowledge of the drug would seem at best a false economy. A glance at the Vademecum International in which manufacturers list and describe their products—and pay for the space they use—will show how consistently members of our Association include the relevant warnings. So far as we know, there is no other sphere of advertising with the same requirement for the regular inclusion of cautionary technical information.

Another example of the cost of safety is the effect of the Schedule G regulations. These provide for stringent controls on the distribution of barbiturate and amphetamine products. They require much more detailed supervision of distribution than with other prescription products—except, of course, narcotics—and more extensive record-keeping.

Some of these and other costs of safety would have to be met by any company handling the products concerned—notably, those costs which result from government regulation. However, there are others which reflect the sense of responsibility and enlightened self-interest of the research-oriented manufacturer. To increase substantially the

supply in Canada of imitative and inferior products handled by firms which do not share such an attitude would seem at best a false economy. In the present developing state of our knowledge about the impact of chemicals on the human body, it could well impair the quality of health care in this country.

PHARMACEUTICAL PATENTS

The Purpose and Value of a Patent System

The three principal purposes of a patent system have been defined by Dr. Vannevar Bush, noted scientist and Nobel laureate, as follows:

> "First, it seeks to stimulate invention and the search for new applications of knowledge. Second, it seeks to promote the introduction into public use of the new devices or processes. Third, it seeks to eliminate secrecy and to make available to others skilled in the field full disclosure of the new ideas."

The value of a patent system in respect to pharmaceuticals can be assessed within two broad categories of function— economic and social. The former relates to the contribution made to economic development, the latter to the therapeutic value of the goods and services that result from the granting of a patent. We propose to consider both these aspects of pharmaceutical patents; to review the impact on them of the present character and administration of the Canadian Patent Act, with specific relation to compulsory licensing under Section 41(3) of that Act; and to suggest certain changes that will, we believe, ensure that patent legislation in this country meets more effectively the true needs of a period of vigorous scientific advance.

Two recent reports, those of the Restrictive Trade Practices Commission and the Royal Commission on Health Services, criticized even the present scale of patent protection for pharmaceuticals. They maintained that either the abolition or emasculation of this protection was a prerequisite for reducing the cost of prescribed drugs. They appear to have based this position on the belief that the consequent wide-open competition in

pharmaceuticals would best serve the national interest. (Royal Commission on Health Services report p. 701 et. seq.)

An effective patent, it is true, confers a temporary monopoly. Thus it rewards the industrialist who makes public the invention, and stimulates working of the patent, which can be assumed to be in the public interest. Introduction of new and effective medicines certainly serves the public interest powerfully and continually. However, when it comes to pricing the product covered by this monopoly, it must be recognized that there are practically no drugs which possess a therapeutic monopoly. For almost every means of treatment, patented or not, there is an alternative, or several alternatives. The existence of these alternatives has a major influence on price levels.

Further, the public interest is not limited to the provision of drugs at the lowest possible price. Quality is extremely important, as is the assurance that these are the safest products which can be devised and manufactured. In addition, physicians should have available a full range of drug preparations for both frequent and rare diseases and conditions, and be well-informed about how and when to use them. The public interest is also far-reaching in time; the flow of therapeutic advances must be stimulated and maintained, progress in pharmaceuticals is at least as important as immediate efficiency. Finally, there is a specific national interest in the growth of a research-based Canadian pharmaceutical industry, making large-scale investments in Canada and offering good employment opportunities.

These are all purposes which can be fostered by a strong patent system

designed to encourage the development and working of inventions in this country.

The Fostering of Industrial Development

A major justification for a patent system is that it fosters industrial development. Canada has recognized that it can enhance its industrial status only if it encourages innovation through research and development. C.M. Drury, Minister of Industry, addressed the Second Ministerial Meeting of Science of the Organization for Economic Co-operation and Development in Paris on January 12, 1966, on "The Role of Government in Stimulating Technical Innovation." He made the following pertinent comments:

> "Our basic premise is that 'technological investment' is the great progenitor of economic growth. Technology enters the economy through the process of innovation, which is one of the most important driving forces of a modern industrial economy. The task facing governments then is to stimulate the innovation process so as to ensure the rapid and effective exploitation of new scientific and technological advances. The solution involves the creation of a favourable climate for innovation and the devising of techniques to promote research and development in industry, where it can be applied for economic purposes.....
>
> "It is sometimes argued that the ready availability of imported technology makes it unnecessary for the smaller nations supporting any substantial R&D activity. A policy of reliance on licensing or imitation is of course much less costly in the short run but carries with it serious limitations on the future viability and growth potential of the dependent industry which thus becomes vulnerable to competition, (both domestic and international). Active engagement in R & D seems the best way of avoiding obsolescence and enabling a firm to successfully assimilate and exploit new technology."

In both its annual reviews published so far the Economic Council of Canada has underlined the need for increased expenditure on research and development. The Second Annual Review of the Council contained the following passage:

> "In our First Annual Review we pointed out that, in order to achieve a satisfactory rate of improvement in productivity and to enhance our competitive position in the world, Canadian industry must be in a position to make adequate use of the rapidly expanding resources of science and technology. In order to do this, we must greatly increase our own efforts in research and development. These greater efforts are necessary so that Canadian industry may be equipped to make the best use of available foreign technology and also to expand considerably its own contribution to new technology to provide a basis for profitable innovation and specialization."

A patent system provides industry with an incentive to innovation. It thereby encourages investment both in research and development and in production facilities, and also fosters the introduction of new products. Patent protection has particular importance for modern research-based industries, of which the pharmaceutical industry is an outstanding example, since their future depends on the ability to incur the high cost of continuing, complex research.

In this connection we quote from a memorandum submitted by the Association of the British Pharmaceutical Industry to the British government on this subject (The Pharmaceutical Journal, January 16, 1965, pp. 52-55):

> "A patent is granted to an inventor by the Crown in exchange for benefits conferred on society by the inventor. If one is to diminish the monopoly granted to a particular group of inventors the group selected should be one that confers upon society a smaller than average benefit. We believe that the pharmaceutical inventor deserves as well of public esteem and reward as does the inventor of any other kind of invention. Yet the inventor of a new drug that for the first time would effectively treat coronary thrombosis is subject to the particular severities of Section 41, whereas the inventor of a new hair curler, machine-gun, whistling top or mouse-trap is not subject to the special provisions of that Section..."

The Nature and Extent of Pharmaceutical Research

We are aware at this point of two counter-arguments relating specifically to the research activity of the Canadian pharmaceutical industry. 1) It is

claimed that the abolition of Canadian patents for pharmaceuticals would have little effect on the expansion of research and development activity within Canada. 2) It has been suggested, notably by the Hall Commission in Recommendation 80, that pharmaceutical research can, and should, be directed and financed by government.

Certainly, the pharmaceutical industry is among the most international of industries, with people throughout the world dependent for life-saving products on the research achievements of other countries. However, expenditure on prescription drug research and development in Canada has been rising steadily. Surveys of our Association members report an increase in R & D expenditure from $2,500,000 in 1959 to $6,500,000 in 1964, and nine companies now have research laboratories in this country.

This expansion is due in part to the research tax incentives offered by the Federal government, and a few companies have been given direct grants for specific projects. An inhibiting influence, however, has been the increase in the past year or two of applications for compulsory licences under Section 41(3), and the apparent ease with which such licences have been obtained.

A company's decision to increase, or even maintain, research expenditure in Canada can be influenced by many factors. An important one is certainly the quality of the scientific community; the relationships the research establishment can develop and the personnel it can employ. Tax incentives and the possibilities of government grants will be taken into account. But attention will also be paid to the climate in which company, laboratory and staff will operate, and here the state of patent protection is a major

influence. In all these matters the advantages in one country will be carefully weighed against those of other possible locations.

If the development of pharmaceutical research is held to be a national interest for Canada, together with the growth of a research-based pharmaceutical industry, the denial to the industry of reasonable patent protection calls for the closest scrutiny. Canada can ill afford decisions that could endanger its long-term interests as a rising industrial power.

The second argument — that pharmaceutical research should be financed by government — ignores the realities of industrial, and notably pharmaceutical, research. This is an increasingly complex and costly activity; several international companies each spend more than $20,000,000 yearly on research and development. Their activities are carried on in close cooperation with universities and hospitals, they form part of an interwoven pattern of scientific exchange, and they are devoted to a specific and essential purpose - the application of scientific and medical knowledge to the development of pharmaceutical products of direct benefit to mankind. But, the fundamental objection is that government-sponsored research is usually isolated from the practicalities of therapeutic necessity and this research therefore cannot be directed economically or effectively without industry cooperation.

Patents, Information and Product Availability

There are significant services performed for Canadians by a research-based international pharmaceutical industry, services intimately linked with the research orientation of that industry, which would be seriously endangered if the treatment of pharmaceutical patents discouraged an orderly pattern of drug development and control. Indeed, on the maintenance of this

pattern depend both the availability and safety of the potent pharmaceuticals used in this country.

Genuine patent protection encourages a company to devote considerable resources to the introduction and marketing of its products. It does this through a carefully planned program of scientifically based information. An imitating company merely takes advantage of the medical information provided by the originating company, and is probably incapable of either maintaining or advancing it.

The activity of the research-based company is a total operation; its professional and experienced personnel are concerned with all its products. The cost of their employment is met largely through the success of a few products, yet their services to the medical profession relate to the totality. There are, indeed, many life-saving and otherwise valuable products enjoying a limited market that a company makes fully available and fully services only because they are part of the total operation. (They are described in Section 8 of this brief). Without reasonable patent protection for its main products, a company might well decide that it could not afford to give this kind of treatment to other important drugs, or, indeed, to introduce new products of however great therapeutic value if they were only used for rare diseases or conditions. Conversely, a study of the applications made for compulsory licences under Section 41(3) will reveal that the applicants, naturally enough, are interested in products which have already obtained substantial sales. Recent licences and applications relate to: Benadryl, Chloramphenicol, Largactil, Dulcolax, Zylocaine, Librium, Stelazine,

Diuril, Hydrodiuril, Stemetil, and Nozinan.

The Protection of Drug Safety

The assurance of drug safety today requires extensive and continuing work in pharmacology and toxicity, beginning with assembly of the material necessary to meet the rigorous demands of a New Drug Submission. We do not believe that an imitating company will possess the scientific resources to fulfil this requirement, or that it can provide the Food and Drug Directorate with the information on which to base manufacturing standards, assay procedures, etc. If the research-based company does not carry out this work, and incur the related expenses, nobody else will. Effective patent protection is the best guarantee Canadians have that all important products resulting from world-wide pharmaceutical and medical research will be introduced in this country.

The difference between the services provided by the research-based and by the imitating company goes still further. The research-based company acquires a great deal of information about the products it markets, and this is always at the disposal of the medical profession and government. It is based upon the use of products of consistent quality. In the event of any problem arising with regard to a drug, such information is of tremendous value in determining both the significance and any remedial action. A company which has merely acquired the right to manufacture or distribute a product will not have the same resources in personnel, clinical experience or accumulated international information. There has been at least one important case where a licensee was completely unable to meet the scientific requirements of government in this

connection. This was brought out in the interrogation of Mr. L.L. Winter of Empire Laboratories Limited by the Special Committee of the Commons on Food and Drugs in November 1964. (Proceedings pp. 375 et seq.)

Crucial in this regard is the decision by the Food and Drug Directorate whether a particular product still has the status of a "New Drug." If the product is still a "New Drug," then the licensee must meet the extensive scientific requirements of a New Drug Submission; if it is not, then the controls which the FDD can exercise are very limited. Because of this technical difference, a very potent drug, one which the originating manufacturer is still subjecting to clinical tests because of significant side effects, would be treated as a comparatively innocuous substance.

The originating company is concerned to keep up-to-date complete information about all indicated uses for all formulations of a product. At the same time, it will collect and evaluate information on negative indications, such as side effects, contra-indications and problems arising from the concurrent use of other medication. Such information is developed out of physicians' reported clinical experience as well as from studies it has, itself, initiated. Uncontrolled compulsory licensing of potent drugs will distort or destroy the validity of much clinical experience; the active ingredient alone does not determine the therapeutic behaviour; reactions can be caused by the formulation as well as the drug.

This danger, indeed the general danger to drug safety, is intensified by the encouragement that Section 41(3) offers to patent infringement. It is a fact, however undesirable, that patent-holding companies hesitate to take action against infringers because the immediate counter-measure

may well be an application for a compulsory licence.

The price of drugs, it is recognized, is— and should be— a matter of public concern. But price cannot be properly considered apart from drug safety, reliability and availability. It is significant that the Special Committee of the Commons on Food and Drugs decided to put drug safety before drug cost when establishing its order of priorities. (Proceedings, pp. 7-8). The public interest is best served when the relationship between price and product or service is in proper balance. Value depends on both the price and the quality of what is purchased.

The Industrial Contribution

Out of a sales volume of $110,465,000 reported by 41 PMAC members for 1964, purchase of goods and services in this country accounted for $85,575,000.

Further evidence of the growing contribution of the pharmaceutical industry to industrial development in Canada is shown by the figures detailing the volume and rate of investment of PMAC members presented in Section 3 of this report.

There is here a solid foundation for future growth— the growth of an industry of vital interest to the people of Canada. It is our contention, however, that continued growth, the expansion of both manufacturing and research establishments, depends on the conditions under which the industry can conduct its business in the years ahead. The state of patent protection may well prove a determining influence.

The Origin of Section 41(3)

It is with this background that Section 41(3) of the Patent Act should be

studied. Section 41(3) discriminates against food and drugs. The question to be considered is whether such discrimination serves the public interest under present circumstances--not a theoretical justification, but the actual results. If, as we believe, it subordinates the real interests of Canadian users of pharmaceuticals to those of a small number of imitative manufacturers, making very large profits out of their licences, then effective remedies for this situation should be implemented.

Section 41(3) was introduced in 1923 (Revised Statutes C.23 s 17 (2)), having been modelled on a similar section in the English Patent Act of 1919 (Patents & Designs Act of 1919, 9 and 10 George V c 80). This English legislation was revised in 1949, with implications that are discussed further along in this section.

The purpose of the original English enactment was explained in the Sargast Committee Report of 1931 in the following terms:

> "During the War it became apparent that Great Britain was suffering from a lack of medicine and drugs, many of which were the subject of patent rights in this country. On the other hand, it was found that in many European countries (e.g. France, Germany, Switzerland) such substances were not capable of protection under the patent laws of those countries. In this state of things it was considered expedient to modify to some extent the monopoly consequent on the existence of patent rights in regard to such substances."

The origin of Section 41(3) was the danger of a shortage of drugs in England. Section 41(3) was enacted to meet a situation which in no way applies in Canada today. In addition, the section was enacted at a time when the pharmaceutical industry, which has become the chief target of compulsory licence applications under the section, was an entirely different industry. The products to which it is now applied are immeasurably more potent and complex, and the requirements of medical

information have correspondingly increased; the research that yielded these products is far costlier; and the continuing research, which present products help substantially to finance, requires an ever greater investment in money and scientific manpower.

The Present Administration of Section 41(3)

The actual wording of Section 41(3), leading to the way it has been administered and to the interpretation placed by courts of appeal on the authority of the tribunal of first instance, intensifies the problem. In effect, both the first and the final decision as to the granting of a compulsory licence are made by the Commissioner of Patents. Well qualified though he is in patent technicalities, he does not have experience either of the economics of the industry or of its medical and scientific aspects. Further, under the present regulations, he is not required to obtain expert advice in these areas. Indeed, the covering letter of the Hilliard Committee Report to the Minister of National Health and Welfare, dated July 12, 1965, made the following observations:

> "It was a shock to the members of the Committee to find the heavy responsibility put on the Commissioner of Patents. Many of the newer drugs are so complicated in their formulae that part of the products, the isomers, might not be active therapeutically though chemically pure, and some dangerous impurities may not be sufficient in amount, in small samples, to be detected.."

Section 41(3) provides that the Commissioner shall grant a licence unless he sees good reason to the contrary. He is thus designated to make the decision whether the exclusive right of a patentee shall become the subject matter of a licence. The courts have refused to interfere with his decision on the ground that the section provides that the decision is one for the Commissioner to make. (Parke, Davis v. Fine Chemicals, 1959 S.C.R.

219: Hoffman-La Roche v. Bell-Craig, 1966 Decision of the Supreme Court of Canada). And the courts have refused to lay down what matters constitute grounds for refusal of a licence.

Section 41(3) is defective in that it contains no objective standard for judgment by the Commissioner. No guidance is given by the section, and no guidance has been given by the courts as to what matters the Commissioner should examine or investigate to determine if good reason does in fact exist for the refusal of a licence.

In the case of Hoffmann-La Roche v. Delmar Chemicals, the Supreme Court of Canada has stated that no decision of the Commissioner has ever been overturned. But no principle has been enunciated by the Court. And significantly, the decision of the Commissioner to grant a licence has never been overturned by the Court on appeal.

Further, both the Exchequer Court and the Supreme Court of Canada have held that the Commissioner is within his right to refuse to grant an oral hearing. It is therefore difficult to see in what circumstances the Commissioner can act without evidence, since the material before him consists of nothing more than blanket statements. The assertions of the applicant are not subject to the test of cross examination.

The problems facing a drug patentee in advancing good reason to the contrary to the Commissioner are demonstrated in the following statement in the Restrictive Trade Practices Commission report:

> "...The Commissioner has not yet been convinced that an applicant was not qualified either financially or professionally,[1] and he

> has rejected all arguments to the effect that the applicant had previously infringed the patent[2] or could not produce economically in commercial quantities[3] or that the market was already adequately supplied.[4] In this respect, the Commissioner of Patents gave the following evidence to the Commissioner (RTPC):
>
> 'Reasons to the contrary being such as the patentee already manufacturing in Canada, public demand being fully supplied, prices being reasonable, the applicant intending to produce only the bulk material leaving to others the tableting, capsuling, compounding, etc., have all been rejected by the Commissioner of Patents in Canada and by the Comptroller General in the United Kingdom (where the law is similar to ours) and the courts have concurred where appeals have been made.'"
>
> (p. 104)

[1] Frank W. Horner Ltd. v. Sharp & Dohme (Can.) Ltd., 15 Canadian Patent Reporter 68; Delmar Chemicals Ltd. v. American Cyanamid Co., 32 Canadian Patent Reporter 40; Micro Chemicals Ltd. v. Societe des Usines Chimiques Rhone-Poulenc, 37 Canadian Patent Reporter 93.

[2] Parke, Davis & Co. v. Fine Chemicals of Canada Ltd., 30 Canadian Patent Reporter, at pp. 66-67.

[3] Delmar Chemicals Ltd. v. American Cyanamid Co., 32 Canadian Patent Reporter 40.

[4] Parke, Davis & Co. v. Fine Chemicals of Canada Ltd., 30 Canadian Patent Reporter, at pp. 65-67; Delmar Chemicals Ltd. v. American Cyanamid Co., 32 Canadian Patent Reporter 40; Charles E. Frosst & Co. v. Carter Products Inc. et al, 29 Canadian Patent Reporter 145.

In the light of these rejections a drug patentee may be pardoned for some perplexity about the intent of the legislation in imposing the limitation that a licence should be refused when good reason to the contrary exists. Indeed, Section 41(3), as it is now administered, appears tantamount to the granting of a licence of right, even though the patentee is fully supplying the market with a product of quality at a reasonable price.

To sum up, Section 41(3) of the Patent Act, subordinates the real interest of Canadians in the availability, quality, and safety of pharmaceutical

products, and in the stimulation of research in one of the most vital areas of human endeavour, to limited and temporary price advantages. This misconception of the real interest would be even more dangerous were the practice of compulsory licensing under Section 41(3) to be extended to drug imports, as recommended by the Hall Commission.

The Establishment of Royalties

There is widespread misunderstanding about the economics of the pharmaceutical industry, especially about the nature and cost of the essential functions performed by a responsible company:

1. Research and development;
2. Manufacturing, including sustained quality control;
3. Presentation to the medical profession, including the maintenance of vital services of scientific information. This requirement—based on a two-way flow of knowledge—goes far beyond the promotional activities usual in other industries.

A pharmaceutical company can maintain these necessary functions only if the prices at which it sells its products cover their cost and yield a reasonable profit. However, as explained above, a company conducts a total operation, and certain overheads cannot be allocated to specific products. In particular, marketed products have to bear the cost of the ongoing research operation, its failures as well as its successes, to pay for future as well as present therapeutic advances.

Unless the holder of a compulsory licence is required to pay a royalty that covers the cost of necessary functions being performed by the patentee,

the licensee is being given something for nothing. This is surely an extreme application of the phrase, "lowest possible price." An examination of the licences which have been granted under Section 41(3) will show that the applications were made in expectation of a "free ride" in relation to certain of these functions. If, indeed, the royalties granted had borne a reasonable relationship to the cost of the functions—a contribution to research and scientific services—it is most doubtful whether the applications would have been pursued.

The Commissioner of Patents has, in fact, interpreted the royalty provisions of Section 41(3) in favour of the applicants. He, himself, made the following statement before the Restrictive Trade Practices Commission:

> "...It seems to me if the price of drugs has been so high, why is it that no more Canadian companies have started manufacturing because, after all, the royalty is a pittance as against the profit that could be made."
>
> (RTPC report at p. 111)

It should be noted that the rate of compulsory licence applications has increased substantially since this evidence was given.

In addition, there is no requirement under Section 41(3) that the licensee should supply the whole of the Canadian market or provide all the types of formulation of a medicine. If he so wishes, he is at liberty to supply only certain areas or certain types of customer, to market only the most profitable items, not, for instance, injectible or liquid preparations for which there may be only a limited demand. Yet the patent-holding company, maintaining a total operation, deems it a responsibility to meet all these requirements.

In the case of Hoffmann-La Roche v. Bell-Craig, the President of the Exchequer Court to a certain degree recognized on appeal the inadequacy of the royalty granted by the Patent Commissioner. The royalty had been established on the selling price of the bulk chemical. The President of the Exchequer Court allowed that it should rather be applied to the selling price of the patented drug in dosage form. His decision included the following finding:

> "I have come to the conclusion that the Commissioner fell into error in thinking that 'the finished material in dosage form, packaged and labelled' was 'outside the scope of the patent' and 'immaterial' to him. On the contrary, the drug in the dosage form, if it is made in accordance with the patented process, is just as much the subject matter of the patentee's monopoly as it is when it is sold in bulk. It is precisely the same product as it is when it is in bulk except that it has been packaged so as to be in the form in which it has value as a merchantable commodity."

In this case, the Commissioner of Patents had granted a royalty of 15 per cent of the selling price of the bulk active ingredient. This would amount to $37.50 per kilogram on a probable selling price of $250 per kilogram. The proposed selling price of the applicant for the finished dosage form amounted to $3,500 per kilogram so that the royalty is equivalent to less than 1 per cent of the patentee's selling price. Since the applicant had done no research and offered little by way of medical information, he would be enjoying substantial profits through obtaining a "free ride" on the essential functions performed by the patentee. It is clear that the scale of compensation awarded the patentee effectively destroys the value of a patent subject to compulsory licensing.

The royalty granted by the President of the Exchequer Court amounted to $525 per kilogram or 15 per cent of the licensee's selling price for the pharmaceutical in finished dosage form. Although this sum would not begin to cover the costs of research and medical information borne by the patentee, it was some recognition of the desirability of awarding the patentee more than a mere pittance.

However, in its judgment delivered on January 25, 1966, the Supreme Court of Canada overturned the decision of the President of the Exchequer Court, returning the royalty to that established by the Patent Commissioner. There is no doubt that the Supreme Court regarded the Commissioner's award as more consistent with the "lowest possible price" referred to in Section 41(3) than the Exchequer Court award. Specifically, it stated that the "maintenance of research incentive", referred to as a royalty criterion in the Supreme Court decision on Parke, Davis v. Fine Chemicals Ltd., had been misinterpreted in the Exchequer Court award.

In effect, recent decisions have created de facto a standard royalty rate for compulsory licences, basing this on a very narrow interpretation of the phrase..."giving the inventor due reward for the research leading to the invention."

By contrast, since 1949 the British Patent Law, source of the Canadian Patent Law, has referred to patentees receiving "a reasonable advantage from their patent rights." Further, the Royal Commission on Patents, Copyright and Industrial Designs (Ilsley Commission) recommended in its report that: "Royalties are from the standpoint of the patentee to be

fixed with reference to reasonable advantage to the patentee instead of due reward for research." (p. 95).

In addition, the Ilsley Commission proposed to strengthen patent protection for drugs by permitting product patents on chemical substances intended for food and medicine, instead of only patents on the process involved, the present situation (p. 93). In contrast, in reversing the Exchequer Court decision in the case of Hoffmann-La Roche v. Bell-Craig, the Supreme Court of Canada came to the following conclusion:

> "The royalty payable by a licensee for using a patented process is one of his costs of production. That being so there is an obvious justification, in cases where a percentage royalty is decided upon, for using as a base the sale price of the bulk material produced by the patented process, rather than a base which reflects a variety of packaging, distribution, promotional, sales and other like expenses."

There appears here a fundamental misunderstanding of the nature of the pharmaceutical industry. The cost of production, the cost of operating the plant, is only one of its continuing and essential costs. The basic purpose of the industry is to provide the means for medical treatment; it is as much a service industry as a manufacturer of goods for retail distribution. In these circumstances, to maintain research and a proper flow of scientific information are two crucial functions.

Essentially, what the applicant for a licence under Section 41(3) seeks is the right to copy the patentee's dosage form so as to claim that this copy has a therapeutic effect identical with the original. In so doing he is, at minimal cost and with no lasting commitment, taking advantage of a substantial market created by the patentee. Further, he relies on

The patentee continuing the necessary efforts and expenditure to support that market. And he will enjoy automatically any benefits that result from any new therapeutic use the patentee may discover, having played no part whatsoever in such discovery. There is no true competition between patentee and licensee since the patentee is in effect continuously subsidizing his competitor. Further, the patentee carries expense burdens immeasurably greater than the licensee's, yet is quite unable to discard them.

The Hilliard Committee Report

Concern about the dangers resulting from the inadequacies of second manufacturers under compulsory licensing led the government to set up last summer a special committee of investigation under Dr. Irwin Hilliard of the University of Toronto.

The report of this committee, tabled May 12, 1966, in the Commons, reiterated this concern and dealt with the hazards which could arise from both compulsory and voluntary licensing. The committee made a number of recommendations, all of which this Association heartily endorses. For reference it is attached as Appendix K.

The recommendations of the Hilliard Committee Report when implemented will do much to protect the public interest so far as drug safety is concerned, but there are, in addition, other vital aspects of the situation that must be dealt with as well. For this reason, our own recommendations regarding pharmaceutical patents would range beyond those of the Hilliard Committee and are covered at the end of this section.

The Potential Role of Sections 19 and 67

In Section 67, the Canadian Patent Act contains effective provisions for action through compulsory licensing to prevent the abuse of a patent: "The Attorney General of Canada or any person interested may at any time after the expiration of three years from the grant of a patent apply to the Commissioner alleging in the case of that patent that there has been an abuse of the exclusive rights thereunder and asking for relief under this Act."

Significant in the definitions of what constitutes abuse is Section 67 (2) (a): "...if the patented invention (being capable of being worked in Canada) is not being worked in Canada on a commercial scale, and no satisfactory reason can be given for such non-working..."

Because of the existence of Section 41(3), no recourse has been had to Section 67 with regard to patents on drugs, yet this section would appear to be the true defender of the public interest. Further, implementation of Section 67 would provide strong encouragement for the extension of pharmaceutical manufactur ng andpharmaceutical chemical manufacturing in Canada. At present Section 41(3) actually discourages manufacturers from working their patents in this country because whether they work them or not has no bearing on the granting of compulsory licences. In this way Section 41(3), as now administered, directly contradicts the normal purposes of patent legislation.

Moreover, Section 19 gives the Government of Canada the right to use any patented invention on payment of reasonable compensation. This provides additional protection for the public interest.

The International Picture

Section 41(3) of the Canadian Patent Act discriminates against pharmaceutical patents in an all-embracing way quite rare in other industrial countries, concerned as they are to make drugs of high quality widely available and also to foster research and industrial expansion. There is nothing similar in the patent law of the United States. Some West European countries have compulsory licensing provisions, but these are generally dependent on abuse of the patent.

While there is now no patent protection for pharmaceuticals in Italy, legislation to reinstate it has been approved by the Council of Ministers and is undergoing parliamentary debate. It will provide process patents of ten years' duration. Compulsory licensing in the public interest is included in the proposed legislation, with the initiative residing in the Minister of Health. Fair compensation is to be paid to the owner of the patent in keeping with the importance of the invention and the profit it is expected to yield. Decisions as to royalty are to be made by the Minister of Health in agreement with the Minister of Industry and Commerce, and there is full appeal to the courts on the matter of royalty.

The draft European Patent Law prepared by the European Economic Community would grant a patent life of 20 years, and permit compulsory licences only in case of proved abuse or where one patent cannot be used without using another. The Council of Europe has made similar recommendations.

In Britain, where Section 41(3) originated, the treatment of the patentee is notably more realistic than in Canada with regard to both the granting of licences and the establishment of royalties. Under the English statute

a licence is not granted as of right to create competition but rather there is a balancing of all factors involved to determine the ultimate public interest. In the event of a licence being granted the royalty is based on the costs of research, medical information service as well as a return on the capital invested in both of these functions. The most recent decisions are J.R. Geigy S.A.'s Patent 1964 RPC 391, and the unreported decisions of the Assistant Comptroller in Farmers Marketing and Supply Company Limited's Patents, 2nd August 1965 and in Pfizer & Co. Inc.'s Patents, Feb. 24, 1966. The latter decision applies the royalty to the patentee's selling price for the product in its dosage form.

Position and Recommendations

We believe that the Patent Act, as it now relates to prescription drugs, does not truly serve the public interest. In contrast, this would be better served by the establishment of new and different procedures.

Our reasons for this position can be summarized as follows:

1. The public interest requires the continuing availability of the products of worldwide pharmaceutical research at reasonable prices. This depends upon the maintenance of invention, product development and distribution, and the diffusion of extensive and reliable information to the medical profession.
2. The public interest also requires that a reward be given for an invention, so that further research is encouraged and the industrialist has an interest in making public the results of the invention. This is the basic purpose of the Patent Act.
3. The public interest therefore does not justify, indeed is opposed to, discrimination against pharmaceutical patents since such

discrimination inhibits the fulfilment of both these purposes.

4. Section 41(3) of the Patent Act, as it is now interpreted and applied, discriminates severely against patents on pharmaceuticals, and so works against the public interest, in the following respects:

   a) It permits compulsory licensing of pharmaceutical patents without setting out any objective standards against which to determine whether the public interest is already being served;

   b) a single individual, the Patent Commissioner, holds almost absolute power to decide whether a licence should be granted, and to determine what royalty should be paid;

   c) it does not provide that the patentee should be adequately compensated for what he loses when a licence is granted;

   d) there is a clear threat to the public health in the proliferation of imitative products introduced without adequate attention to the scientific capabilities of the manufacturer or distributor, capabilities which should go far beyond the ability to manufacture to minimum standards.

5. Section 67 of the Patent Act contains full provision for compulsory licensing where a patent is not being worked or is otherwise abused. In addition, Section 19 allows for the over-riding interest of the Government of Canada.

6. Effective application of Section 67 would serve as a strong incentive to the expansion of pharmaceutical and pharmaceutical chemical manufacturing in Canada, since it treats the non-working of a patent as grounds for compulsory licensing. This incentive does not exist under Section 41(3).

In the light of these facts, we make the following recommendations:

1. The protection of the public interest requires the establishment of a properly qualified tribunal to decide on compulsory licence applications in the first instance. This tribunal should be composed of men able to pass judgment on legal matters, economic arguments and medical and scientific implications.

2. It should be clearly stated what matters this tribunal will take into account during its review of a licence application, including the elements to be considered in arriving at an equitable royalty.

3. A compulsory licence should be granted on economic grounds only if the tribunal finds that the patent is being abused or not used for the public interest.

4. There should be full right of appeal from the decisions of the tribunal, with a definite determination of the bases on which an appeal can be made, regarding both the licence itself and the royalty granted.

5. <u>There should be an early revision of the Patent Act, leading to the establishment of a tribunal with the composition and powers outlined above.</u>

THE QUESTION OF "GENERIC EQUIVALENCY"

There are two ways of designating a pharmaceutical chemical—by its lengthy chemical appellation, and by what has come to be known as the proper, nonproprietary, common or generic name. This is derived from the chemical appellation. A brand name, however, fulfils a different function. It establishes the manufacturer's responsibility for a particular drug product.

An editorial, published in the Journal of the American Medical Association of November 9, 1964, concluded its comments on "Drug Names" with the following advice:

> "The preface of the second booklet published by the USAN (United States Adopted Names) Council in February, 1964, states: 'Teaching in pharmacy and medicine requires a common designation especially for a drug that is available from several sources. Nonproprietary names greatly facilitate communication between physicians ...' So it is that physicians should be encouraged regularly to use nonproprietary names, recognizing, however, that such usage is solely for educational purposes and does not provide assurance of the quality and potency of products prescribed.
>
> "To enlarge on the latter point, the physician who prescribes meprobamate as such has no way of knowing that his patient will receive the drug in a form of highest quality and expected potency. Careful prescription writers provide the necessary assurance in one of three ways: by writing the nonproprietary name plus the name of a manufacturer known to be reliable; by writing the desired brand name; or by writing the nonproprietary name plus the desired brand name. The third method has the modest advantage of reducing the likelihood that the pharmacist will make a mistake in filling the prescription.
>
> "When a physician uses a brand name or a manufacturer's name to designate the source of supply, he is fulfilling a part of his professional obligation to his patient. Having decided that medication is required, he should assume the responsibility for selecting a manufacturer who will supply the drug in a therapeutically effective form at the lowest possible cost to the patient."

The members of our Association and most other Canadian companies market most of their products under brand names. In so doing, they follow the general international pattern of the industry. There are also a smaller number of companies which market products according to the generic name of the active ingredient, though some, in the interests of their company reputation, find it necessary to mark the drugs with a company identification, and use advertising and salesmen to promote the products of their particular company. This was acknowledged by Mr. L.L. Winter of Empire Laboratories Limited in his evidence before the Special Committee of the Commons. (Proceedings p. 381)

Both the Restrictive Trade Practices Commission and the Hall Commission called for wider generic prescribing by Canadian doctors—in order to reduce the cost of drugs. Certain questions are raised here.

The Scope of Generic Prescribing

Only a certain proportion of prescription drugs—those containing a single active ingredient or named in a recognized pharmacopoeia—can be sold easily by generic name. Studies in this connection were presented to the Hall Commission by the Canadian Pharmaceutical Association (Brief pp. 39-40). They show that about half the prescription products available are mixtures, and only about a quarter have so-called generic equivalents. In some cases, the latter are also brand-name products. In this connection, it should be noted that in many instances—and for a variety of reasons—a pharmacist will fill a generic prescription with a brand-name product.

Experience of Purchasing by Price Alone

Hitherto, government, hospitals and other institutions have been the main purchasers of drugs by generic name, it being assumed they possessed the means to ensure quality. However, as Dr. Showalter of the Department of Industry testified before the Special Committee of the Commons, the government has had its troubles with products bought by price alone. "The practice of competitive bidding on price seems to have resulted in obtaining supplies mainly from the least competent or possibly the least scrupulous suppliers." (Proceedings p. 416) This was the origin of the decision to develop the CGSB standards for companies wishing to tender for government business. Related concern about the quality of prescription drugs available to the public led the Committee to recommend that all manufacturers and distributors be registered so that they can be inspected by the Food and Drug Directorate. The Committee also commented that, "It is known that so-called generic firms present greater problems for the Food and Drug Directorate." (Proceedings p. 517)

Highly relevant, too, is the evidence given by Dr. K.J.R. Wightman, Professor of Medicine at the University of Toronto, to the Special Committee of the Commons, describing on behalf of his hospital why "we are not buying large amounts of the generic kind of thing." (Proceedings pp. 403-409)

The Fate of Alberta Bill 107

In April 1962 the Alberta government passed a bill that enabled pharmacists to substitute generic-name equivalents for brand-name products

unless specifically ordered not to by the physician. This legislation has had little or no impact. According to "Drug News Weekly" of February 15, 1964, Donald Cameron, Registrar of the Alberta Pharmaceutical Association, has stated that about 88 per cent of the doctors in the province prescribe by brand name. He is quoted as follows: "Doctors are wary of prescribing generics because there have been too many reports of cases where cheaper drugs were used without success or with disappointing results, thus eventually increasing the overall cost."

The Limits of FDD Action

Registration of manufacturers and the strengthening of the Food and Drug Directorate -- both proposed by the Special Committee of the Commons -- would certainly lessen the danger of poor-quality drugs finding their way onto the Canadian market.

But it should also be recognized that government inspection can never guarantee the quality of all drugs sold in Canada. This was explained by Dr. C.A. Morrell, then Head of the FDD, in his appearance before the Special Committee of the Commons:

> "... I am loath to have people say that a drug is guaranteed by the Food and Drug Directorate. I do not see how we can guarantee it. There are many subtleties, and we have not the facilities to detect differences..... You cannot put 'government approved' on a drug."
>
> (Proceedings p. 158)

A major weakness in the Hall Commission approach to prescription drug services is its failure to appreciate the inevitable limitations on governmental action. This is most evident in the section of the Hall Commission report entitled "Quality of Drugs" (pp. 366-370). An analysis

of that section is attached as Appendix K.

A Sound Approach

It is our belief that open competition between qualified suppliers is the best way to serve the interests of the Canadian people where drugs or any other products are concerned. Such competition is not encouraged by the destruction of long-accepted methods of protecting the legitimate rights of the manufacturing companies. Further, safety and progress should be factors of paramount importance in the development of policies regarding the pharmaceutical industry. Special care needs to be taken to ensure that firms producing or distributing drugs do contribute to these purposes, and are capable of meeting the resulting responsibilities.

The requirements for sound drug purchasing were described by Dr. C.A. Morrell, when he was serving as Chief of the Food and Drug Directorate:

> "When it comes to buying top-quality drugs, the things to check are the ability, facilities, personnel and conscience of the drug manufacturer. Neither a brand name nor a drug's generic name is the sole reliable guide to quality. The real point is who makes the drug and how it's made--the control system that ensures careful and scientific testing for potency and reliability."
>
> (Globe & Mail, August 18, 1960)

Is there Such a Thing as Equivalency?

We have discussed the safety considerations involved in the generic drug question. There is also the broader question of whether any two prescription drug products, even though containing the same active ingredient, can be considered truly equivalent. Long experience, backed by considerable scientific evidence, leads our companies to believe that this is rarely the case.

The preponderance of brand name prescribing by Canadian physicians would seem to validate this point of view. And in his evidence before the Royal Commission on Health Services, Dean F.N. Hughes of the School of Pharmacy of the University of Toronto made this statement:

> "We believe the principle of requiring practitioners to prescribe medicine only by chemical or generic name to be entirely wrong. This presupposes that any given dosage form containing the same quantities of a drug will have the same clinical effect. It has been clearly shown that this does not necessarily follow." (p. 9945)

The many factors of product formulation which can affect therapeutic efficiency were reviewed succinctly in an article by Dr. Max S. Sadove et al. which appeared in the February 1965 issue of American Professional Pharmacist. This is attached as Appendix M.

The practising physician should certainly be informed about the cost of therapy as he is about its effectiveness, and we support the Hall Commission recommendation for more extensive efforts in this area. However, maintenance of the physician's freedom to prescribe the drug of his choice is of over-riding importance. In this connection, we would cite the forceful statement made by the Hinchliffe Committee in Britain, many of whose views have been reprinted with approval by the Hall Commission:

> "The clinical and academic freedom of the general practitioner must be maintained. The loss of self-respect consequent on any departure from the principle, which has been accepted as fundamental to the National Health Service in this country, that a doctor can prescribe any drug which he considers necessary for his patients, would lower the status of the profession and ultimately have an adverse effect on the whole medical service provided for the patient. The doctor must be the sole judge of his patient's requirements for treatment." (p. 62)

THE PROVISION OF PRESCRIBED DRUGS UNDER MEDICARE AND WELFARE PROGRAMS

There is growing interest throughout Canada in the provision of prescribed drugs as part of medical service plans, whether for the population as a whole or for people in receipt of welfare assistance. The Hall Commission recommended a Prescription Drug Benefit, which would require contributory payments and be based on a National Drug Formulary. Certain provinces have lately made new arrangements for the provision of drugs to their citizens on welfare, while others are working on broad plans for prescription prepayment or insurance.

As stated in the introduction to this brief, "we believe it axiomatic that in a country which has attained the general standard of living of Canada no citizen should go without needed medication because he cannot afford it." We would point out, however, the importance of every Canadian receiving pharmaceutical products which meet "the highest standards of safety, reliability and therapeutic effectiveness." The range and quality of the preparations doctors may prescribe, whether for patients as a whole or for a particular class of patient, should depend solely on therapeutic considerations. (Our reasons for this position are presented in the preceding section.)

It would scarcely be logical for government to develop plans designed to assure all citizens of the physician's services they need, and then limit the means of treatment the physicians may prescribe. In view of the comparative size of the national expenditures on physicians' services and prescribed drugs as documented by the Hall Commission (this brief Section 1,) such a policy may well be described as spoiling the ship

for a ha'porth of tar.

With these major purposes in mind, our Association has formulated and made public the following set of nine principles that should govern, we believe, the provision of prescription drugs under health service programs:

1. It is the responsibility of the pharmaceutical manufacturer in co-operation with the professions of medicine and pharmacy to search, develop and provide safe and effective drugs of the highest quality.
2. It is a co-operative responsibility of the manufacturer and the pharmacist to make safe and effective medications of high quality immediately available in all parts of Canada.
3. It is the right of the physician to prescribe the drug preparation of his choice.
4. Nothing must be allowed to interfere with the duty of the pharmacist to respect the integrity of the physician's prescription.
5. It is the citizen's right to consult the physician of his choice.
6. It is the citizen's right to have his prescription dispensed by the pharmacist of his choice.
7. It is the responsibility of any agency paying for drugs to recognize the rights and duties of the physician, the pharmacist and the citizen.
8. The respect of industrial property rights as represented by patents and trade marks is the essential foundation for progress in research and therapeutics.
9. A pharmaceutical benefits program which assists the needy and encourages

the self-supporting to provide for themselves will best meet the requirements of the people of Canada.

These principles set out a general framework. We have made specific proposals relating to the provision of drugs for welfare recipients to the governments of British Columbia and Quebec. In these, we offered our co-operation in determining through survey and analysis the exact incidence of different types of drug requirement as a basis for cost control. We suggested a system for obtaining a rebate of the Federal sales tax on products dispensed to welfare patients, since such products are effectively purchased by the provincial government. Finally, we reported that, although the Association could not legally commit its members to any pricing policies, many of them had expressed a willingness to place their experience at the disposal of public health authorities.

So far as the general provision of prescribed drugs is concerned, we have worked with the Canadian Pharmaceutical Association in developing its proposals for Pharmacare, and we consider this an effective plan for meeting the real needs of the large majority of Canadians.

RECOMMENDATIONS RELATING TO THE COST OF DRUGS

In general, we consider that the prices charged for the prescription drugs made and sold by our member companies are fair and reasonable as evidenced by information in Section 4. These are products of the highest quality, the fruits of intense and continuing international research. Their proper availability across Canada depends on sustained programs of medical information and promotion, and on a nation-wide distribution network. Those who manufacture and distribute the drugs must meet the costs of doing business in Canada with regard to salaries, wages and the purchase of materials, goods and services.

In this connection, we would draw attention to the following statement by the Hall Commission:

> "We conclude on the basis of the evidence presented to us that it is the unequal and generally unpredictable incidence of heavy drug costs that have given rise to the greatest concern on the part of the public, rather than what has been described as the 'high costs' of drugs as such." (Report, p. 355.)

We have, however, a number of recommendations bearing on the cost of drugs. Some of these would reduce the price of drugs generally, or the prices of certain products, or the prices to certain groups of citizens. Others would convey to the professions concerned and the general public more extensive and precise information about the cost of particular products.

1. We strongly support the recommendation made by many groups and individuals that the Federal sales tax on prescription drugs be abolished. This would reduce the manufacturer's prices by approximately 10 per cent.

2. There is a clear requirement for much wider availability of programs for drug insurance or prepayment. These would greatly assist the relatively small number of Canadians who find buying prescription drugs a real burden, whether due to personal circumstances or to the impact of either catastrophic or chronic illness. As reported in Section 13, a joint study has been made by PMAC and CPhA of the feasibility of prescription drug insurance, and a model insurance plan has been developed. Such a program would satisfy the requirements of most Canadians, and provide an effective vehicle through which government can help those who need assistance. (See Appendix N.)

3. As mentioned in Section 9 of this brief, we support the establishment of an independent source which would provide doctors and pharmacists with accurate and up-to-date information about pharmaceutical products. The size of companies' expenditures on medical information and promotion relates directly to the effectiveness of these activities. Should such a foundation prove to have a significant influence on the prescribing habits of physicians, its activities might well modify the extent of promotional activity.

4. Recommendation 82 of the Hall Commission calls for the development of more comprehensive and up-to-date statistics relating to the cost of drugs and expenditures on drugs. We believe that the provision of more detailed and more broadly-based statistics would be helpful to all who are concerned with the development of drug benefit programs, and would generate valuable information for the general public. We would be happy to work with the Dominion Bureau of Statistics or other

authorities in the elaboration of such a program.

5. We favor a cooperative program by the universities, medical and pharmacy associations, and pharmaceutical manufacturers to provide physicians with more extensive information about the cost to their patients of particular drug therapies. In fact, some companies now include information about the approximate cost of therapy in their medical literature.

6. The Association approves the action taken by some member companies to abolish suggested catalogue prices for drug products available only on prescription, leaving the retail pharmacist to assess the sum necessary for the proper compensation of his services. In this connection, we acknowledge the support given increasingly by representatives of retail pharmacy to a cost-price-plus-professional-fee system for pricing prescriptions. This system generally has the effect of increasing somewhat the price of the cheaper prescriptions but markedly reducing the price of those prescriptions most often criticized as being unduly expensive.

7. The Hall Commission has recommended that the Government of Canada, assisted by the Drug Advisory Committee, sponsor jointly with the drug industry and such provincial governments as wish to participate, a study of the feasibility of a voluntary drug price restraint program for Canada, for implementation on a trial basis for a period of five years. (Recommendation 73, Report p. 43) The members of our Association stand willing to enter into any discussions about the prices of their products which the governments concerned should consider desirable.

We would, however, reiterate our position that such negotiations must take cognizance of the nine principles set down in Section 13.

PHARMACEUTICAL MANUFACTURERS ASSOCIATION OF CANADA

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Ottawa 4, Ontario.

MEMBERSHIP APPLICATION FORM

Pharmaceutical Manufacturers Association of Canada is an incorporated national association of companies engaged in manufacturing and distributing pharmaceutical products prescribed or used by the medical profession. The principal aim of the Association is to advance the interests of pharmaceutical manufacturers. Its objectives are:

To promote and encourage the inter-change of knowledge and ideas for the betterment of the pharmaceutical manufacturing industry and its services;

To foster mutually constructive and satisfactory trade relations and to maintain and improve public relations;

To co-operate with legislative committees, government departments and agencies, medical and pharmaceutical societies, and other bodies in respect to matters affecting the pharmaceutical manufacturing industry;

To promote among the members of the Association a spirit of friendly co-operation, thereby striving for cordial intra-industry relations.

Membership is by election. Applicants for membership are required to abide by the Association's Principles of Ethics, Code of Marketing Practice, By-Laws, and other rules and regulations which may be in force from time to time.

In addition, applicants are required to offer evidence to the effect that they have been inspected by and qualify under the PMAC Standards on Manufacture and Quality Control.

There are two membership categories:

FULL MEMBERS: Corporations or firms which manufacture and distribute, or distribute under their own labels, in Canada, under proper conditions for control of quality and standards, pharmaceutical preparations dispensed or prescribed by physicians.

ASSOCIATE MEMBERS: Corporations or firms which do not distribute pharmaceutical preparations under their own labels in Canada but which either manufacture pharmaceutical preparations in dosage form for others or supply the pharmaceutical chemicals for use in making pharmaceutical preparations. Firms or corporations engaged in scientific research with the intention of distributing pharmaceutical preparations under their own labels in Canada are eligible for election to associate membership on an annual basis until such time as they commence distributing under their own labels in Canada and thus become eligible for full membership.

Where the parent company is located outside of Canada, membership is open to the Canadian subsidiary or branch only; the Canadian address of such subsidiary or branch only shall be carried on the official roster of the Association.

PMAC Membership Application

NOTE: The following questions apply only to the company's pharmaceutical operations, and not to other lines of manufacturing in which the applicant may be engaged.

Please check the boxes applicable: ☐

PART I

1. Name and address: _____

_____

2. State names of principal officers or partners: _____

_____

_____

3. State addresses and types of branch offices in Canada: _____

_____

_____

4. State when business of applicant was established: _____

5. State whether this application is for:

Full Membership ☐ or Associate Membership ☐

6. Check function of your organization in Canada:

Production ☐ Distribution ☐ Packaging ☐ Custom Manufacturing ☐

Fine Chemicals ☐

7. (a) State whether your products sold in Canada are manufactured by:

The Canadian Company ☐ Parent Company ☐ Associated Company ☐

Custom Manufacturer ☐

(b) If your products are made by one or more custom manufacturers, state names of all companies doing such work for you:

_____

_____

_____

8. State channels through which goods are distributed:_____

_____

_____

9. State number of employees in Canada: Total _____

Production _____ Sales _____ Packaging _____ Other____

10. (a) State whether your company qualifies for sales to government under Canadian Government Specifications Board Standard 74-GP-1a, and has passed government inspection for this purpose:

YES ☐ NO ☐

(b) If "No", explain reason in covering letter.

(c) If your company has qualified, please attach to this form a copy of the letter of compliance which you have received from the Federal Government.

PART II

NOTE: The following questions in Part II apply to the Canadian operations of a company which manufactures on its own premises in Canada, or to the parent company operations of a non-manufacturing company which is a subsidiary of a foreign corporation.

11. (a) State whether the following questions in Part II apply to:

The Canadian Company ☐ or Parent Company ☐

(b) If Parent Company, state name, city and country where located:

_____

12. (a) State name and qualifications of full time employee responsible for production:

_____

(b) To whom does he report (executive position):

_____

13. (a) State name and qualifications of full time employee responsible for quality control:

_____

(b) To whom does he report (executive position):

_____

14. On a blank sheet, to be attached to this application, give a brief description of the Production and Quality Control administrative organization of your company. Indicate separate departments, such as manufacturing, packaging, engineering, maintenance, etc. In addition list the number of employees on each group mentioned, and indicate those who are technically trained.

15. State the type of products manufactured:

Oral ☐ Parenteral ☐ Topical ☐ Veterinary ☐ Other ☐

16. State whether you perform your own analytical work in the control of your products:

	Yes	No
(a) Chemical	☐	☐
(b) Sterility	☐	☐
(c) Biological	☐	☐
(d) Microbiological	☐	☐

17. If the answer to any part of question 16 is "No", describe the facilities employed:

_____

_____

_____

18. State which department in your company is responsible for each of the following functions:

	Function	Company Department
(a)	Raw materials specifications:	_____
(b)	Release of raw materials for manufacturing use:	_____
(c)	Establishment of formula:	_____
(d)	Establishment of manufacturing procedures:	_____
(e)	In process control of manufacturing procedures:	_____
(f)	Packaging materials specifications:	_____
(g)	Finished package specifications:	_____
(h)	In process control of packaging procedures:	_____
(i)	Release of products for distribution:	_____
(j)	Disposition of returned merchandise:	_____

PART III

19. Are you willing to have your premises inspected by a special committee of the Association Yes ☐ No ☐

20. State whether you subscribe to and agree to abide by the following, and kindly place your signature opposite each item:

(a)	The P.M.A.C. Principles of Ethics:	_____	_____
(b)	The P.M.A.C. Code of Marketing Practice:	_____	_____
(c)	The P.M.A.C. By-Laws:	_____	_____
(d)	Other P.M.A.C. rules and regulations which may be in force from time to time:	_____	_____

21. Kindly attach to this application two copies of a catalogue or descriptive list of your company's products.

Signed by: _____
Name of Chief Executive Officer

_____ _____
Date Title

FOR PMAC OFFICE USE ONLY

Received _____ Approved _____

Checked _____ Category _____

Inspected _____ Date _____

CGSB _____

Pharmaceutical Manufacturers Association of Canada

PRINCIPLES OF ETHICS

Every member subscribes to the following principles of ethics and undertakes to abide by them:

I

The calling of a pharmaceutical manufacturer is one dedicated to a most important public service, and such public service shall be the first and ruling consideration in all dealings;

II

The pharmaceutical manufacturer must produce his preparations only under proper conditions and with scrupulous faithfulness to required standards of quality;

III

Preparations must be labelled and merchandised only in a manner free from misrepresentation, misleading practices of all kinds and in entire harmony with the highest standards of commercial morality and professional ethics;

IV

In his dealings with his fellow manufacturers and in his dealings generally, the pharmaceutical manufacturer shall be actuated by a sense of fairness and justice and his conduct shall in every way be consistent with honourable business practice. More particularly, he shall refrain from misappropriating the trade names of others, or their formulae or the distinctive form or dress of their products. He shall also refrain from making false or disparaging statements about his competitors or their products;

V

Pharmaceutical manufacturers must constantly and conscientiously strive to advance the science and elevate the calling of manufacturing pharmacy to the highest plane of public value, to the end that it may best and most completely serve the medical profession and the public.

Pharmaceutical Manufacturers Association of Canada

CODE OF MARKETING PRACTICE

The PMAC Code of Marketing Practice consists of four sets of standards, which govern drug advertisements directed to the medical profession, conduct for medical service representatives, hiring and training of medical service representatives, and hospital activities of medical service representatives. These various standards are attached to this preamble.

The three sets of standards governing the conduct, hiring and training, and hospital activities of medical service representatives, were prepared by the PMAC Marketing Section and adopted by the Board of Directors on January 21, 1965.

The Standards Governing Drug Advertisements Directed to the Medical Profession were prepared by the PMAC Government Relations Division and the Marketing Section, and were submitted to the membership for vote by ballot. They were adopted by the Board of Directors on January 21, 1965, and are to become effective on January 1, 1966.

Following is a review of the principles behind these various standards.

Pro Omnibus

Pharmaceutical research would be of little value if the results of this research were not made widely known to the professions concerned. It is, therefore, essential that the medical and allied professions be promptly, fully and reliably informed of the existence and properties of the medicines which are available for them to prescribe, use or supply. The pharmaceutical manufacturing industry is an important source of information on therapeutic developments resulting from its research and, as a consequence, must be free to disseminate information on its products, based on ethical considerations as identified in this Code.

Recognizing our responsibility to the public welfare and our obligations to the medical and pharmaceutical professions, we, the members of the PMAC, pledge ourselves to the following principles of ethical drug marketing.

General Provisions

Marketing activities include the spoken as well as the written word, direct mail and journal advertising, films and any other medium used for the communication of information on medical specialties.

1. Claims for the usefulness of a product shall be based on acceptable, scientific evidence, and should reflect this evidence accurately and clearly.

2. Medical claims and assertions contained in promotional communications shall have medical review and approval prior to release.

3. Prompt, complete, and accurate information concerning therapeutic agents shall be made available to the medical and pharmaceutical professions.

4. Quotations from medical literature, or from the personal communications of clinical investigators in promotional communications, shall not change or distort the true meaning of the author.

5. The release to the lay public of information on the clinical use of a new drug or to a new use of an established drug, prior to adequate clinical acceptance and presentation to the medical profession, is not in the best interests of the medical profession or the lay public.

6. Reference to other manufacturers or their specialties shall be restricted to a factual comparison.

Journal Advertising and Promotional Literature

1. The advertising practices of member companies are based on the desire to impart product information and knowledge and are governed by provisions as stated in the foregoing General Provisions.

2. Policies of member companies with regard to direct mail advertising and journal advertising are individual and reflect the marketing practices of the companies concerned. All members agree that such promotion should in no way be offensive to the physician and should conform to the high ethical standards of the profession.

3. Guided by regulations of the Food and Drug Directorate, advertising material containing scientific and technical information should give doctors and members of allied professions as complete a picture as possible of the properties of the product, based on current scientific knowledge.

4. All member companies agree to abide by the PMAC Standards Governing Drug Advertisements Directed to the Medical Profession, a copy of which is attached.

Medical Conventions

Member companies attending any medical or allied convention shall abide by the Medical Exhibitors' Association's regulations and recommendations, to which PMAC subscribes.

Medical Service Representatives

In their desire to maintain the best relationship with the health professions, member companies of PMAC and their medical service representatives are governed by the standards comprising the Code of Marketing Practice.

Pharmaceutical Manufacturers Association of Canada

Standards Governing Drug Advertisements Directed to the Medical Profession

For the purpose of these standards "advertisement" means any representation made to the medical profession through the media of:

(1) Medical journal advertising.

(2) Books and publications directed to the medical profession where the manufacturer has jurisdiction over the material appearing. e.g., Vademecum International and similar books of reference.

(3) Direct mail advertising.

An Advertisement Containing Therapeutic Claims Must Include Clearly and Concisely:

(1) The official, proper or chemical name of the drug.
(2) A quantitative list of the medicinal ingredients contained in each dose or unit.
(3) The recommended dosage, method of use and route of administration.
(4) A reference to side effects, precautions and contra-indications of the drug in the recommended dosage and a statement that detailed information of these is available on request.
(5) Any precautionary statement required by the Food and Drug Directorate relating to the pharmacological action of the drug.
(6) The name of the advertiser.

In addition:

(7) Claims for the usefulness of a product must be based on acceptable scientific evidence and must reflect this evidence accurately and clearly. A claim made within quotation must conform to the same standards as a claim not presented in the form of a quotation.
(8) In the case of a new drug or one upon which considerable clinical experience has not been accumulated, it must not be stated categorically that the drug has no side effects or toxic hazards.
(9) Advertising copy should reflect an attitude of caution particularly with respect to the use of drugs which have not been studied for prolonged periods.
(10) Statements and illustrations made in promotional material should be in good taste and should present the facts in an unequivocal manner.

Any infringement of these Standards Governing Drug Advertisements Directed to the Medical Profession will be considered a breach of PMAC Principles of Ethics and dealt with accordingly.

The above regulations do not apply to advertisements of a reminder type for an established product, providing such advertisements contain no recommended dosage or therapeutic claims but are restricted to a general statement as to class or kind of medication, e.g., analgesic, antibiotic, anti-depressant, etc. Such reminder advertisements must, however, include the following:

(a) Proper or official name.

(b) The statement "Full information is available on request."

(c) Company name.

(d) A brief reference to Food & Drug Directorate warnings when these warnings are directed to the medical profession. It is not necessary to repeat the warning in full and it is not necessary to refer to warnings directed to the public.

Pharmaceutical Manufacturers Association of Canada

Standards of Conduct for Medical Service Representatives

The Medical Service Representative shall by his conduct reflect high professional and moral standards at all times, so that he may be a credit to the pharmaceutical industry and favourably influence the members of the medical and pharmaceutical professions. He will agree to maintain the standards of conduct as specified by the PMAC.

1. Appearance

   He will be neat, clean and well groomed and will dress according to professional business standards. His literature, samples, bag, car, etc. will also reflect the high standard of neatness and cleanliness expected of his person.

2. Attitude

   He will reflect pride in his profession and his company, and support them with facts in any discussions which may arise during or after business hours.

3. Reliability

   He will carry out all commitments and promises and make them only within the confines of the policies of his company.

4. Vocabulary

   He will use no profanity but maintain the level of language of his professional customers and his voice will be modulated so as not to offend patients or customers.

5. Honesty

   He will be honest in all his dealings and should provide professional contacts with full and factual information on his products, with no attempt at misrepresentation or exaggeration.

6. Accuracy

   His statements must be accurate and complete and must not mislead either directly or by implication. His product knowledge should be maintained at a level which will enable him to fluently converse with the professions and supply necessary information on his products. His assertions must be scientific and backed up with medical evidence. Such professional standards of honesty and accuracy are to be maintained at all times so that a high professional stature will be accredited to the individual sales representative, his company and the industry as a whole.

7. Deportment

He will observe the conventions of courtesy to competitors as he would to his customers. He will not initiate discussion of a competitive product by name, or criticize a competitive product, company or its personnel. He will observe the usual courtesies such as:

(a) Smoking only on invitation in the doctor's office, pharmacy or hospital.

(b) Sitting down only when invited to do so in the doctor's office.

(c) Placing his detail bag on the floor only, and in a non-traffic area.

(d) Applying no forceful tactics to interview doctors in their offices or at hospital and convention exhibits or any other place such as hallways, etc., which could be classified as "buttonholing the doctor".

(e) Avoid offering inducement or employing subterfuge to gain an interview with a doctor or pharmacist.

(f) He should acquaint himself with office, store and hospital protocol, and adhere strictly to any special ruling which he may encounter.

(g) Observing the precedence principle that if a competitor is already in a doctor's office, the representative shall depart until completion of business, unless he has an appointment or local conditions dictate otherwise.

(h) Yielding his seat to patients in a crowded physician's office or hospital.

(i) His contact with patients and customers should be socially and professionally above reproach.

(j) Addressing the physician formally as Doctor, preferably by name (such as Dr. Jones) in the presence of other physicians and associated personnel no matter how well he knows the doctor, unless the doctor indicates otherwise.

(k) Refraining from walking into doctors' private offices, or prescription departments, without permission.

(l) Removing his hat when entering a doctor's office or a prescription department.

(m) Departing from competitors' exhibits on the approach of a physician.

(n) Observing the rules of the Medical Exhibitors Association at medical conventions.

Pharmaceutical Manufacturers Association of Canada

Standards of Hiring and Training of Medical Service Representatives

The Medical Service Representative symbolizes his company and the pharmaceutical industry in the eyes of the medical and pharmaceutical professions. To ensure that the Medical Service Representative is qualified and trained for this role, the following Standards of Hiring and Training should be followed:

1. It is desirable for a representative to be a university graduate and that he be required to submit proof of this standing.

2. It will be found helpful if the applicant for the position of medical service representative is interviewed on different occasions by two or more responsible individuals within the company and, if possible, one of these interviews is held in the applicant's home with his wife present.

3. The prospective employer should thoroughly investigate the applicant's character and personal life.

4. It will be helpful for the company to utilize various aids which are available to assist in screening applicants, e.g., aptitude and intelligence tests, retail credit investigation, etc.

5. Prior to employment, it would be desirable to have the applicant work one or two days with one of the company's better representatives, in order to field test the applicant on interest and adaptability to the job.

6. Before employment, the applicant should be required to pass a medical examination.

7. All references submitted by the applicant, particularly those of former employers should be carefully checked prior to employment.

8. An extensive period of supervised training, in both the classroom and the field should be given every representative following employment. This training will vary with different companies but should be long enough to give the representative adequate background information and training to enable him to properly present the technical aspects of his company's products.

9. Indoctrination into the principles of ethics and standards of performance and conduct should be included in all training programs.

10. Member companies are urged to implement supervised training programs in the field for all representatives.

11. Member companies are urged to implement periodic refresher courses for all representatives.

12. Member companies are asked to encourage their representatives to undertake courses of study and self-improvement, aside from the training provided by the company, such as the Dale Carnegie Course, salesmanship courses, Toastmasters' Club, etc.

13. Member companies should encourage representatives to enter into community activities.

Pharmaceutical Manufacturers Association of Canada

Standards Governing Hospital Activities of Medical Service Representatives

Aims of the Standards

1. To establish methods whereby Medical Service (Pharmaceutical) Representatives can provide information and service to physicians, pharmacists, medical staff and hospital officials in hospitals,

   and

2. To establish methods whereby problems of mutual interest may be discussed and solved as they arise.

With full realization that procedures usually vary with the policy and organizational structure of each institution, the following Standards are prepared for guidance. The Pharmaceutical Manufacturers Association of Canada will endeavour to have these Standards uniformly adopted and every effort will be made to guard against infractions:

1. Hospital Policy

   (a) The representative should see the written hospital policy for pharmaceutical representatives where one exists. If a written hospital policy is not available, the representative should complete the hospital's Interview Form when requested by the chief pharmacist or appropriate administrative officer.

   (b) Representatives should be aware of the policies of each hospital and follow them carefully.

2. Attitudes and Deportment

   (a) Representatives should conduct themselves as guests of the hospital at all times in carrying out hospital work, and no attempt should be made to attract undue attention.

   (b) Every effort must be made to avoid interference with normal activities of the hospital staff. Promotional work should be carried out in a pleasant and courteous manner.

   (c) A physician who does not wish to enter into conversation should not be forced to do so by a representative.

   (d) Although no restrictions are placed on the normal detailing of physicians, the members of the Pharmacy and Therapeutics Committee should not be detailed in their official capacity without prior consultation with the Chief Pharmacist.

3. Appointments

(a) Appointments should be made prior to visits if it is the custom of the hospital.

(b) Under no circumstances should an individual physician be summoned through the hospital "locating" system, unless prior permission has been obtained. In any event, the representative should always identify both himself and his company.

4. Sampling

(a) Representatives should be guided by hospital and Food and Drug Directorate regulations in distributing samples. Under no circumstances are samples of drugs to be given to unauthorized personnel.

(b) If investigational drug material or clinical trial drugs or samples to be used on hospital patients are given to a physician by a pharmaceutical representative, the representative should inform the Chief Pharmacists of the hospitals where the physician has privileges when possible.

5. Hospital Exhibits

(a) Scheduling more hospital exhibits than are allowed by existing regulations should be avoided.

(b) Notices of exhibits should be placed on hospital bulletin boards only after receiving the approval of the proper hospital officials. Residents, interns and nurses should be invited to visit the exhibit only after obtaining the permission of the proper hospital official.

(c) The assigned arrival and departure times should be followed carefully.

(d) An exhibit suitable for the space available should be used, and set up without disturbing normal routine, or calling for assistance.

(e) The representative should remain at the exhibit. The exhibit should be kept neat and tidy at all times.

(f) A physician should not be approached directly. The interview should be initiated only if the physician voluntarily visits the exhibit.

(g) All waste paper should be removed and furnishings returned to their original position before leaving the hospital. If at all possible, the hospital official permitting the exhibit should be thanked personally.

(h) Representatives should follow the hospital policy as to products and literature to be displayed.

NOTE: These Standards have been prepared following consultation with a committee of the Canadian Society of Hospital Pharmacists.

The Role of the Detailman

Each year our Association undertakes a survey of the number of detailmen employed by member companies and their remuneration and conditions of service. The latest survey shows that 49 companies employed 1,799 detailmen. For the industry as a whole there appears to be about one detailman for every ten physicians. We understand that in the United States and the United Kingdom the figure is in the same range. A proportion of the detailmen employed by our member companies are, however, wholly or largely occupied in working with hospital and retail pharmacists. In general, 40 per cent of detailing time, it is estimated, is spent on calls to hospital staffs and to pharmacists.

A survey conducted by MRC Limited for MD of Canada in 1963, based on interviews with 200 English-speaking physicians across Canada, showed that 98 per cent saw some at least of the detailmen who called on them, with the average number of detail calls received being 11.5 per month, and the average length of time spent with a detailman 13 minutes. A survey conducted in England in 1964 by Research Services Limited, based on interviews with 245 doctors, showed that 73 per cent had seen all the detailmen who called on them. They reported seeing an average of 4.8 detailmen in a two-week period.

The detailman fulfils a number of functions, the emphasis varying according to company and product. Primarily he is the channel of communication between his company and the medical profession. He brings doctors information and literature about products, answers questions within the limits of his training and knowledge, referring to the medical staff those he cannot answer. He relays back to the company any incidents the doctor may report regarding side effects or unusual reactions to his company's products. He also secures signatures for the samples which physicians request. A number of companies employ specially trained and experienced representatives for liaison work with hospital staffs.

The value of the detailman as a two-way channel of communication cannot be over-emphasized, particularly as in many instances he is acting as the representative of a world-wide organization. The information he provides will have international backing, and that which he acquires can have implications for many countries besides Canada.

The pharmacy side of the detailing job has a number of elements: provision of information about new products, so that the pharmacist will be prepared for the first prescriptions; checking on stocks and in particular making sure that any products with expiry dates have been replaced in time; promotion of over-the-counter products, and the arrangements of suitable point of sale advertising; keeping the pharmacist up to date on company developments.

Should a drug withdrawal ever be required, or a serious warning about any of the company's products, the detailman has a mammoth job to inform as rapidly as possible both physicians and pharmacists in his

territory. His activity will, of course, be supplemented by printed communications.

MD Attitude to Detailing

Physicians generally welcome the detailman system. This does not mean that they receive all the detailmen who call on them. A minority, notably specialists in the larger cities, will not receive any detailmen at all. Others are selective in the time they spend — based on the company, the product, and the man, himself. Similarly, many hospitals have strict regulations about when and how detailmen can call on the medical and other professional personnel. The MRC survey quoted above reported that 23 per cent of physicians screen detailmen in some way. As to the attitude to detailing, 60 per cent said detail calls were welcome, 16 per cent unwelcome, and 24 per cent were neutral or expressed no opinion. On a related question, 68 per cent said detail calls were informative, 14 per cent said they were uninformative, and 18 per cent were neutral or expressed no opinion.

The Research Services Survey from England asked doctors the following question: 'The range of drugs and pharmaceutical products is continually increasing. How do you yourself keep up to date with new developments?' The following were the six major sources listed:

Articles in medical journals	71 per cent
Manufacturers' representatives	36 per cent
Discussion with colleagues	25 per cent
Manufacturers' literature sent through the post	24 per cent
Prescribers Journal (an official publication)	21 per cent
Advertisements in medical journals	18 per cent

No recent similar survey from the United States has come to our attention. However, a comprehensive survey of the Attitudes of U.S. Physicians toward the American Pharmaceutical Industry was published in 1959. It was the work of Ben Gaffin and Associates, and financed by the American Medical Association. It asked these three related questions:

> So many new drugs are being developed today that it is getting harder for a physician to keep current. Which two or three of the sources listed do you find most important to you personally in familiarizing yourself with new drugs?
>
> Which two or three of those sources would you say are probably most effective with most doctors?
>
> Which two or three sources on the list would you say are probably least effective with most doctors?

This part of the questionnaire yielded the following results:

	Most Important Personally	Most Effective Generally	Least Effective Generally
Detailmen	68 per cent	65 per cent	5 per cent
Journal papers, articles	40	30	7
Medical journal ads	32	26	18
Direct mail	25	23	35
Doctor conversations	24	19	10

Education and Training of the Detailman

What are the detailman's qualifications for his work? Just over 40 per cent of those working for members of our Association have university degrees, predominantly in pharmacy, and 72 per cent have had some university training. The breakdown by academic background for those with university degrees may be summarized as follows:

Pharmacy Degrees	40%
Other Science Degrees	26%
Bachelor of Arts Degrees	20%
Bachelor of Commerce Degrees	8%
Post-Graduate Degrees	2%
Other Degrees	4%
	100%

The proportion of detailmen with university degrees is generally higher the larger the detailing force. The following table summarizes the picture for four company categories:

No. of Detailmen	No. of Companies	Total No. of Detailmen	No. with Un. Degrees	Percentage with Un. Degrees
1 - 20	12	137	47	34%
21 - 40	13	404	101	25%
41 - 60	10	499	220	44%
61 & over	7	500	260	52%

Fifty per cent of the detailmen employed by members of our Association have previous selling experience before joining their companies and 20% have retail or hospital pharmacy experience. Nevertheless, all of them receive pre-field training which may be for one week or may be for as long as six months. This pre-field training is supplemented by refresher training which, in 75% of our member companies, is given at regular intervals. The other companies provide additional training when it appears warranted by the detailman's performance in the field or by his performance in a written examination set by the company.

The basic training is designed to acquaint the detailman with many aspects of pharmaceutical operations, including medical background in the area of his company's products, the ethical presentation of the products, to physicians and pharmacies, Government Food & Drug Regulations, territory management, and company sales policies and procedures. The

refresher courses cover much the same material on a higher and more sophisticated level. Attention is also given to the pharmacological and therapeutic aspects of new products introduced since the previous course and to improving the effectiveness of detailmen in presenting product information to the physician. The training covers so many aspects of pharmacy and medical knowledge that after five years with his company the detailman is a professional in his field and looks for security and compensation compatible with his level of competence and experience.

Compensation

The compensation of a sales representative of a pharmaceutical company is normally divided into two parts: (i) a base salary and (ii) a commission or bonus over and above the base salary. A combination of salary and commission was the manner of remuneration in 3 of the 45 companies included in the survey; salary and bonus in 26 companies; salary, commission and bonus in 8 companies. Of the remaining eight companies, one paid by commission only, six paid by salary only, and one by salary plus prize points.

As might be expected, a salesman's salary is higher the longer his service with his company. Average rates of compensation, by length of service, are summarized in Exhibit 1. Also shown are the range of base salary and gross compensation and the modal (most frequent) value. From this Exhibit, it can be seen that the average starting salary in 1964 was $5378. The average salesman with over 10 years service received a base salary of $7910 in that year. Average base and gross compensation in 1964 may be summarized as follows:

Years of Service (1)	Average Base Salary (2)	Average Gross Compensation (3)	Commission etc (3)-(2) (4)	Commission as % of Av. Gross Comp. (5)
Hiring	$5378	-	-	-
Under 2 yrs.	5741	$6192	451	7.28%
2 - 5 yrs.	6394	7157	763	10.66
5 - 10 yrs.	7118	8067	949	11.76
Over 10 yrs.	7910	8915	1005	11.27

Exhibit I

Average Base Salary and Gross Compensation

of Detailman in 1964

Period of Service	No. of Companies	Average	High	Low	Mode
(1) Average Base Salary					
Hiring	43	$5378	$6000*	$4380	$5400
Under 2 yrs.	43	5741	6701*	4463	5700

Period of Service	No. of Companies	Average	High	Low	Mode
2-5 years	44	$6394	$7512*	$4517	$6300
5-10 years	42	7118	8743	5472	7500
Over 10 years	34	7910	10180	5714	8000

(2) Average Gross Compensation

Under 2 years	37	$6192	$7340*	$5199	$6300
2-5 years	39	7157	8885*	5700	6920
5-10 years	38	8067	11113	6460	7500
Over 10 years	30	8915	11401	6364	8900

* Note:

One company reported average compensation as follows:

Average base salaries	-	Hiring	$8000
		Under 2 years	9500
		2-5 years	10500
Average gross compensation	-	Under 2 years	10700
		2-5 years	11400

Although these figures were the highest in their categories, they have been excluded from the above table as the company has only 4 employees and is not representative of the group.

Source:

P.M.A.C. 1964 Survey of Salesmen's Compensation

Cost to the Company

The figures already cited show the average and range of compensation of the detailman. The cost to the company varies depending on the distribution of salesmen by years of service. It is clear that the longer a salesman stays with a company, the higher his salary and commissions become. Accordingly, his cost to his company also increases.

The 45 companies in the 1964 survey reported a total employment of 1643 detailmen. The distribution of these men by years of service was as follows:

Years of Service	No. of Detailmen	% of Total
Under 2 years	483	29.40%
2-5 years	424	25.81

Years of Service	No. of Detailmen	% of Total
5-10 years	393	23.91
Over 10 years	343	20.88
	1643	100.00

When this distribution is applied to the average base salary and gross compensation, the weighted average cost of a detailman to the typical company becomes:

Base salary	6692
Commission	766
Gross Compensation	7458

It may thus be concluded that the average gross cost of a detailman to his company, excluding expense allowances and overhead, was $7458 in 1964.

It is important to bear in mind that these figures are only averages, so that the cost to any one company may be quite different from this figure. The rate of gross compensation may differ from the average and a company may have a preponderance of salesmen with short service or lengthy service, thereby yielding a cost different from the weighted average.

On the latter point, however, it is to be noted that only 9 companies had no salesmen with over 10 years service; 1 had none with over 5 years; 2 had none with 5 to 10 years; and 1 had none with less than 2 years service. The majority of companies had salesmen in all the "length of service" categories.

Other Costs

In addition to salary and/or commission, all companies in the survey reported that their detailmen had an expense account and automobile allowance. The average expense account was reported at $1599 for the year and the average annual cost of a car at $1653. When these costs are added to the gross compensation, the average detailman cost his company $10710 in out-of-pocket costs in 1964.

These costs may be summarized as follows:

Gross Compensation	$7458
Travel & other Expenses	1599
Automobile	1653
	$10710

When an adjustment for fringe benefits and other overhead is added to these figures, it is safe to say that the average detailman cost his company $16,000 in 1964.

PHARMACEUTICAL MANUFACTURERS ASSOCIATION OF CANADA

1964
ANNUAL STATISTICAL SURVEY

TOTAL RESOURCES EMPLOYED
41 COMPANIES

ASSETS		Total 1 $	Human Pharmaceuticals 2 $	All Others 3 $
1.	Cash	6,944,444	5,532,258	977,929
2.	Accounts and Notes Receivable	25,945,552	18,265,033	6,909,858
3.	Inventory	31,399,366	19,789,317	10,342,316
4.	Land, Plant and Equipment	49,679,493	40,163,716	8,518,288
5.	Accumulated Depreciation	17,286,385	13,719,936	3,332,414
6.	All other Assets	9,787,109	7,847,880	1,525,120
7.	TOTAL ASSETS	106,469,579	77,878,268	24,941,097

INCOME STATEMENT - TOTAL COMPANY OPERATIONS

41 COMPANIES

	Total	Packaged Human Pharma-ceuticals	All Others Including Bulk Human Pharma-ceuticals
	1	2	3
	$	$	$
REVENUES			
1. Sales (Federal Sales and Excise Taxes not included)	148,053,720	107,784,504	40,269,216
2. Other Income	2,806,174	2,680,892	125,282
3. TOTAL REVENUE	150,859,894	110,465,396	40,394,498
EXPENSES AND TAXES (Except Sales and Excise Taxes)			
4. Cost of Goods Sold	63,816,758	35,399,032	28,417,726
5. Distribution (Including Warehousing)	6,322,984	4,254,333	2,068,651
6. Marketing	38,536,666	32,286,618	6,250,048
7. R and D	7,269,492	7,119,529	149,963
8. Royalties	3,569,651	3,367,893	201,758
9. Administration	14,640,454	11,586,050	3,054,404
10. Interest Charges	381,058	309,435	71,623
11. Income Taxes	8,586,848	8,115,632	471,216
12. TOTAL EXPENSES AND TAXES	143,123,911	102,438,522	40,685,389
13. Net Earnings	7,735,983	8,026,874	(290,891)
14. Dividends (Subtract)	2,127,900	1,873,374	254,526
15. Earnings Retained	5,608,083	6,153,500	(545,417)

APPLICATION OF THE REVENUE DOLLAR FROM HUMAN PHARMACEUTICAL SALES

41 COMPANIES

		Foreign	Canadian	Total
		1	2	3
		$	$	$
1.	Materials	13,680,107	14,786,285	28,761,662
2.	Salaries, Wages and Benefits	172,266	29,058,712	30,130,268
3.	Depreciation	4,002	1,822,857	1,895,904
4.	Taxes	4,602	6,941,397	7,027,146
5.	Interest	159,318	151,962	350,555
6.	Public Services	4,394	688,817	708,585
7.	(a) Management Services Charges (Net after deduction of withholding tax)	2,253,732	21,831	2,298,663
	(b) Withholding Tax	36,485	62,727	99,212
8.	(a) Royalties (Net after deduction of withholding tax)	2,512,928	382,882	2,965,619
	(b) Withholding Tax	210,477	214,793	435,961
9.	(a) Dividends (Net after deduction of withholding tax)	1,011,923	630,397	1,690,236
	(b) Withholding Tax	82,389	100,999	184,138
10.	Other Expenses	1,935,279	25,010,953	27,398,058
11.	Earnings Retained	147,463	4,523,256	3,846,075
	TOTAL	22,215,365	84,397,868	107,792,082

HUMAN PHARMACEUTICALS
COST OF GOODS SOLD
41 COMPANIES

		$
1.	MATERIAL (cost including freight)	
	(a) Imported From Unrelated Company	2,755,956
	(b) Imported From Related Company	10,983,239
	(c) Canadian Purchases From:	
	(i) Related Companies	1,765,538
	(ii) Other PMAC Companies	2,028,248
	(iii) Others	7,380,068
	(d) Duties	1,656,242
2.	LABOR	4,178,105
3.	PLANT COSTS	4,795,567
	TOTAL	35,542,963

MARKETING EXPENSES

41 COMPANIES

		Total for Year $	Physicians' Information $	Other $
1.	(a) Field Selling Expense (Including supervisory and representatives' salaries, living expenses, cars, meetings, equipment etc.)	16,844,633	12,176,598	4,668,035
	(b) Administration of Marketing, Selling and Advertising Function (Management and staff services, home office salaries and other expenses of the marketing department, including marketing research)	4,694,395	3,567,047	1,127,348
	(c) Advertising and Promotional Expenses	11,438,533	9,980,869	1,457,664
	TOTAL	32,977,561	25,724,514	7,253,047
2.	How much Did You Spend on the Following During the Year:			
	(a) Medical Exhibits and Space	229,357	190,958	38,394
	(b) Medical and Pharmaceutical Journal Advertising	2,331,527	2,118,005	213,522
	(c) Direct Mail Advertising	2,739,423	2,509,965	229,458
	(d) Samples (This refers to promotional samples only and does not include assay samples, etc.)	3,939,446	3,702,215	237,231
	(e) Other:			
	(i) Product	1,704,459	1,299,882	404,577
	(ii) Non-Product	494,321	331,645	162,676
	TOTAL	11,438,533	10,152,670	1,285,858

R AND D EXPENSES
37 COMPANIES

1.	Of Total R and D What Was the Amount Actually:	
	(a) Spent in Canada	5,504,323
	(b) Charged to the Canadian Company by Related Company Outside of Canada	1,579,140
	(c) Paid to Non-Related Organizations Located Outside of Canada	8,703
	SUBTOTAL	7,092,166
	(d) Give a Reasonable Estimate of the Cost of R and D, Performed on your Behalf by Related Companies, But For Which No Charge Is Made	5,439,303
	TOTAL	12,531,469
2.	R and D Laboratory Expenses	4,820,833
	Clinical Investigation (Including medical department)	1,917,169
	R and D Grants (Exclude clinical research grants)	436,232
	TOTAL	7,174,234

EMPLOYMENT

38 COMPANIES

Ph.D.	D.Sc.	M.D.	M.A., M.Sc. or Equal	B. Pharm. B.Sc. or Equal	B.A.	B. Com.
106	3	71	92	884	192	105

TOTAL EMPLOYMENT: 6098

INTERNATIONAL DRUG PRICES (1)
in Domestic Currency Units

Product	Strength	Pkg. Size (Canada)	CANADA Price to Ret.	U.S. Price to Ret.	U.K. Pounds Price to Ret.	ITALY Lire Price to Ret.	GERMANY DM Price to Ret.
Achromycin	250 mg. Caps	16	3.24	2.90	0.77	1,680	15.81
Chloromycetin	250 mg. Caps	16	3.96	5.10	0.68	992	18.21
Terramycin	250 mg. Caps	16	4.17	3.63	0.93	2,225	15.81
Penbritin	250 mg. Caps	16	5.37	4.40	1.29	3,180	25.86
Gantrisin	500 mg. Tabs	100	4.14	2.94	0.800	2,029	9.51
Decadron	0.5 mg. Tabs	100	11.94	9.67	3.19	-	29.33
Librium	10 mg. Caps	100	7.20	7.00	1.000	2,221	11.60
Equanil	400 mg. Tabs	50	3.40	2.90	0.315	-	6.96
Stelazine	2 mg. Tabs	50	3.75	3.93	0.875	967	9.25
Ismelin	10 mg. Tabs	100	4.33	6.80	1.383	1,412	7.58
Hydrodiuril	25 mg. Tabs	100	3.12	3.80	1.48	-	12.90
Diuril	500 mg. Tabs	100	4.38	6.00	1.600	-	22.96
Peritrate	10 mg. Tabs	100	2.50	2.50	0.258	1,200	2.82
Doriden	0.5 gm. Tabs	100	3.97	4.00	-	1,615	10.20
Seconal	0.1 gm. Tabs	100	2.85	2.16	0.300	2,389	10.75
Pyribenzamin	0.5 gm. Tabs	50	1.53	1.40	-	588	6.15
Banthine	0.05 gm. Tabs	100	5.76	4.32	-	-	8.20

(1) Canadian prices include sales tax.

APPENDIX F

INTERNATIONAL DRUG PRICES (1)
in Domestic Currency Units

Product	Strength	Pkg. Size (Canada)	FRANCE FRANKS Price to Ret.	HOLLAND GUILDERS Price to Ret.	SWEDEN Kroner Price to Ret.
Achromycin	250 mg. Caps	16	-	15.76	16.36
Chloromycetin	250 mg. Caps	16	9.06	7.07	7.46
Terramycin	250 mg. Caps	16	15.06	12.50	16.40
Penbritin	250 mg. Caps	16	27.88	20.06	-
Gantrisin	500 mg. Tabs	100	14.18	14.34	13.20
Decadron	0.5 mg. Tabs	100	39.53	18.09	31.90
Librium	10 mg. Caps	100	16.92	15.00	15.60
Equanil	400 mg. Tabs	50	5.93	4.08	4.33
Stelazine	2 mg. Tabs	50	-	-	-
Ismelin	10 mg. Tabs	100	24.30	7.90	12.32
Hydrodiuril	25 mg. Tabs	100	-	12.69	19.00
Diuril	500 mg. Tabs	100	-	20.14	31.25
Peritrate	10 mg. Tabs	100	4.75	2.68	-
Doriden	0.5 gm. Tabs	100	-	-	-
Seconal	0.1 gm. Tabs	100	-	9.46	9.77
Pyribenzamin	0.5 gm. Tabs	50	5.90	-	7.40
Banthine	0.05 gm. Tabs	100	-	15.12	19.32

INTERNATIONAL DRUG PRICES IN CANADIAN DOLLARS (1)

Product	CANADA Price to Ret.	U.S. Price to Ret.	U.K. Price to Ret.	ITALY Price to Ret.	GERMANY Price to Ret.
Achromycin	3.24	3.11	2.31	2.89	4.27
Chloromycetin	3.96	5.48	2.04	1.71	4.92
Terramycin	4.17	3.90	2.79	3.83	4.27
Penbritin	5.37	4.73	3.87	5.47	6.98
Gantrisin	4.14	3.16	2.40	3.49	2.57
Decadron	11.94	10.39	9.56	-	7.92
Librium	7.20	7.52	3.00	3.82	3.13
Equanil	3.40	3.11	.94	-	1.88
Stelazine	3.75	4.22	2.62	1.66	2.50
Ismelin	4.33	7.30	4.14	2.43	2.05
Hydrodiuril	3.12	4.08	4.43	-	3.48
Diuril	4.38	6.44	4.79	-	6.20
Peritrate	2.50	2.69	.77	2.06	.76
Doriden	3.97	4.30	-	2.78	2.75
Seconal	2.85	2.32	.90	4.11	2.90
Pyribenzamin	1.53	1.50	.84	1.01	1.66
Banthine	5.76	4.64	-	-	2.21

Exchange Rates: "Monthly Bulletin of Statistics," August 1965, United Nations, Table 62, p. 173-179.
1964 Rates were given in USA Dollars; converted into Canadian currency equivalents as follows:

USA $	.93 :	$ Can
Canada $	1.00 :	"
Francs	4.56 :	"
Lire L	581.7 :	"
D-Mark	3.70 :	"
Guilder	3.34 :	"
Pound UK	.334:	"
Kroner	4.79 :	"

(1) Canadian prices include sales tax.

APPENDIX F.3

INTERNATIONAL DRUG PRICES IN CANADIAN DOLLARS

Product	FRANCE Price to Ret.	HOLLAND Price to Ret.	SWEDEN Price to Ret.
Achromycin	-	4.71	3.41
Chloromycetin	1.99	2.11	1.56
Terramycin	3.30	3.74	3.42
Penbritin	6.11	6.00	-
Gantrisin	3.11	4.29	2.75
Decadron	8.67	5.41	6.66
Librium	3.71	4.49	3.25
Equanil	1.30	1.22	.90
Stelazine	-	-	-
Ismelin	5.33	2.36	2.57
Hydrodiuril	-	3.79	3.96
Diuril	-	6.02	6.52
Peritrate	1.04	.80	-
Doriden	-	-	-
Seconal	-	2.83	2.04
Pyribenzamin	1.29	-	1.54
Banthine	-	4.52	4.03

Hours of Labour Required to Buy Selected Drugs in Eight Countries *

Product	CANADA Hours	U.S. Hours	U.K. Hours	ITALY Hours	GERMANY Hours	FRANCE Hours	HOLLAND Hours	SWEDEN Hours
Achromycin	1.60	1.15	2.21	4.50	4.24	-	6.62	2.30
Chloromycetin	1.96	2.02	1.95	2.66	4.88	3.17	2.97	1.05
Terramycin	2.06	1.43	2.67	5.96	4.24	5.26	5.25	2.30
Penbritin	2.66	1.74	3.71	8.52	6.93	9.75	8.43	-
Gantrisin	2.05	1.16	2.30	5.44	2.55	4.96	6.02	1.85
Decadron	5.91	3.82	9.15	-	7.86	13.82	7.60	4.34
Librium	3.56	2.77	2.87	5.95	3.11	5.92	6.30	2.19
Equanil	1.68	1.15	.90	-	1.87	2.07	1.71	.61
Stelazine	1.86	1.55	2.51	2.59	2.48	-	-	-
Ismelin	2.14	2.69	3.97	3.78	2.03	8.50	3.32	1.73
Hydrodiuril	1.54	1.50	4.25	-	3.46	-	5.33	2.67
Diuril	2.17	2.37	4.59	-	6.15	-	8.46	4.39
Peritrate	1.24	.99	.74	3.22	.76	1.66	1.13	-
Doriden	1.97	1.58	-	4.33	2.73	-	-	-
Seconal	1.41	.85	.85	6.40	2.88	-	3.97	1.37
Pyribenzamin	.76	.55	.80	1.58	1.65	2.06	-	1.04
Banthine	2.85	1.71	-	-	2.20	-	6.35	2.71

TABLE I

*The above hours have been computed with reference to the price to retailer.

Index of Labour Hours Required to Buy Selected Drugs in Eight Countries Based on the Price to the Retailer

PRODUCT	CANADA	U.S.	U.K.	ITALY	GERMANY	FRANCE	HOLLAND	SWEDEN
Achromycin	100.	71.88	138.13	281.25	265.00	-	413.75	143.75
Chloromycetin	100.	103.06	99.49	135.71	248.98	161.73	151.53	53.57
Terramycin	100.	69.41	129.60	289.30	205.81	255.32	254.84	111.64
Penbritin	100.	65.41	139.47	320.27	260.50	366.50	316.88	-
Gantrisin	100.	56.58	112.19	265.36	124.39	241.95	293.66	90.24
Decadron	100.	64.64	154.82	-	132.99	233.83	128.59	73.43
Librium	100.	77.78	80.59	167.08	87.33	166.23	176.90	61.52
Equanil	100.	68.45	53.57	-	111.30	123.20	101.78	36.31
Stelazine	100.	83.33	134.94	139.24	133.32	-	-	-
Ismelin	100.	125.68	185.48	176.60	94.84	397.12	155.11	80.83
Hydrodiuril	100.	97.40	275.95	-	224.66	-	346.07	173.36
Diuril	100.	109.21	211.51	-	283.39	-	389.84	202.29
Peritrate	100.	79.83	59.67	259.66	61.29	133.86	91.12	-
Doriden	100.	80.20	-	219.79	138.57	-	-	-
Seconal	100.	60.28	60.28	453.89	204.25	-	281.55	97.16
Pyribenzamin	100.	72.36	105.26	207.88	217.09	271.03	-	136.83
Banthine	100.	59.99	-	-	77.18	-	222.76	95.07
AVERAGE	100.	79.15	129.40	243.00	168.88	235.08	237.46	104.31

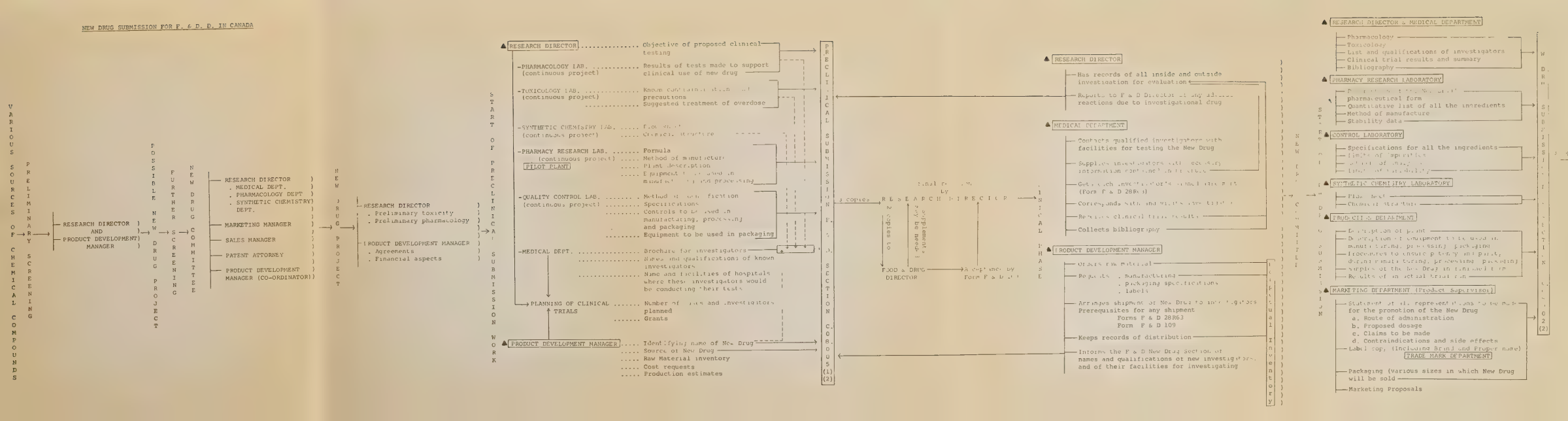
TABLE II

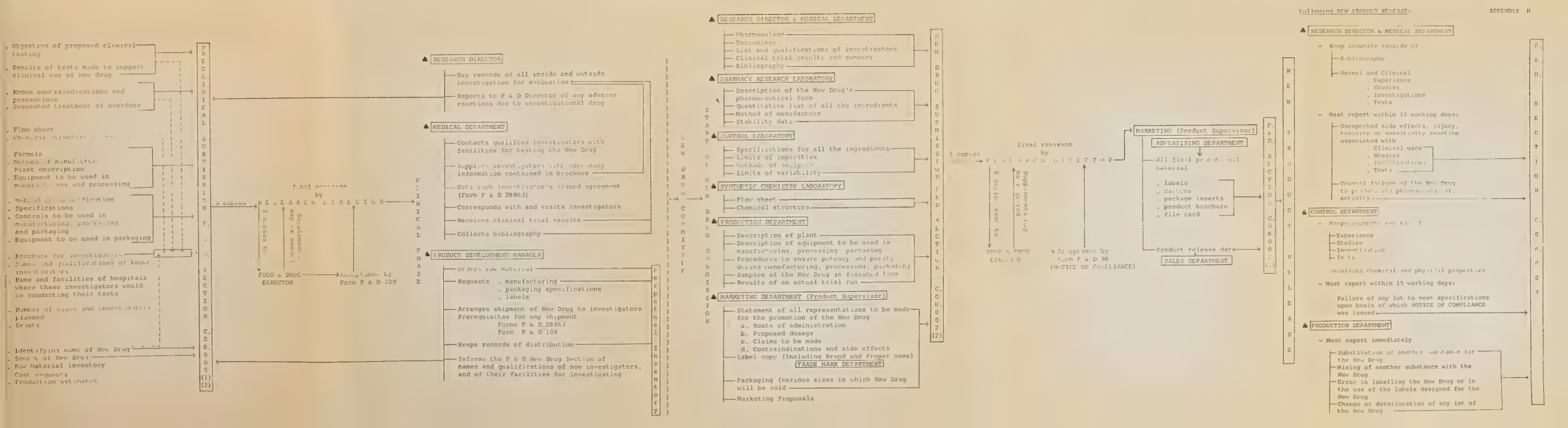
COST OF QUALITY CONTROL

34 COMPANIES

		1963
A.	Cost of operating quality control laboratories	$ 1,777,352
B.	Additional quality control costs required to meet PMAC standards.	1,180,108
C.	Quality control costs deriving from line or in process inspections	574,655
D.	Manufacturing cost of goods sold as already reported (human pharmaceuticals)	35,541,982

NEW DRUG SUBMISSION FOR F. & D. D. IN CANADA




PRECLINICAL SUBMISSION F. & D. SECTION C.08.005 (1) (2)
. Objective of proposed clinical testing
. Results of tests made to support clinical use of new drug
. Known contraindications and precautions
. Suggested treatment of overdose
. Flow sheet
. Chemical structure
. Formula
. Method of manufacture
. Plant description
. Equipment to be used in manufacturing and processing
. Method of identification
. Specifications
. Controls to be used in manufacturing, processing and packaging
. Equipment to be used in packaging
. Brochure for investigators
. Names and qualifications of known investigators
. Name and facilities of hospitals where these investigators would be conducting their tests
. Number of cases and investigators planned
. Grants
. Identifying name of New Drug
. Source of New Drug
. Raw Material inventory
Cost requests
. Production estimates
3 copies
RESEARCH DIRECTOR
final revision by
2 copies to
Supplements may be required
FOOD & DRUG DIRECTOR
Acceptance by Form F & D 109
CLINICAL PHASE
NEW DRUG COMMITTEE
RESEARCH DIRECTOR
Has records of all inside and outside investigation for evaluation
Reports to F & D Director of any adverse reactions due to investigational drug
MEDICAL DEPARTMENT
Contacts qualified investigators with facilities for testing the New Drug
Supplies investigators with necessary information contained in brochure
Gets each investigator's signed agreement (Form F & D 28R63)
Corresponds with and visits investigators
Receives clinical trial results
Collects bibliography
PRODUCT DEVELOPMENT MANAGER
Orders raw material
Requests . manufacturing
. packaging specifications
. labels
Arranges shipment of New Drug to investigators
Prerequisites for any shipment
Forms F & D 28R63
Form F & D 109
Keeps records of distribution
Informs the F & D New Drug Section of names and qualifications of new investigators, and of their facilities for investigating
Perpetual Inventory
START OF NEW DRUG SUBMISSION
RESEARCH DIRECTOR & MEDICAL DEPARTMENT
Pharmacology
Toxicology
List and qualifications of investigators
Clinical trial results and summary
Bibliography
PHARMACY RESEARCH LABORATORY
Description of the New Drug's pharmaceutical form
Quantitative list of all the ingredients
Method of manufacture
Stability data
CONTROL LABORATORY
Specifications for all the ingredients
Limits of impurities
Methods of analyses
Limits of variability
SYNTHETIC CHEMISTRY LABORATORY
Flow sheet
Chemical structure
PRODUCTION DEPARTMENT
Description of plant
Description of equipment to be used in manufacturing, processing, packaging
Procedures to ensure potency and purity during manufacturing, processing, packaging
Samples of the New Drug in finished form
Results of an actual trial run
MARKETING DEPARTMENT (Product Supervisor)
Statement of all representations to be made for the promotion of the New Drug
a. Route of administration
b. Proposed dosage
c. Claims to be made
d. Contraindications and side effects
Label copy (Including Brand and Proper name)
TRADE MARK DEPARTMENT
Packaging (various sizes in which New Drug will be sold
Marketing Proposals
NEW DRUG SUBMISSION FILED SECTION C.08.002 (2)
3 copies
RESEARCH DIRECTOR
final revision by
2 copies sent to FOOD & DRUG DIRECTOR
Supplements may be required
Acceptance by Form F & D 98 (NOTICE OF COMPLIANCE)
MARKETING (Product Supervisor)
ADVERTISING DEPARTMENT
All final printed material
. labels
. cartons
. package inserts
. product brochure
. file card
Product release date
SALES DEPARTMENT
F. & D. SECTION C.08.007
NEW PRODUCT RELEASE
Following NEW PRODUCT RELEASE:
APPENDIX H
RESEARCH DIRECTOR & MEDICAL DEPARTMENT
- Keep accurate records of
Bibliography
Animal and Clinical
. Experience
. Studies
. Investigations
. Tests
- Must report within 15 working days:
Unexpected side effects, injury, toxicity or sensitivity reaction associated with
. Clinical uses
. Studies
. Investigations
. Tests
Unusual failure of the New Drug to produce its pharmacological activity
CONTROL DEPARTMENT
- Keeps records re the
Experience
Studies
Investigation
Tests
involving chemical and physical properties
- Must report within 15 working days:
Failure of any lot to meet specifications upon basis of which NOTICE OF COMPLIANCE was issued
PRODUCTION DEPARTMENT
- Must report immediately
Substitution of another substance for the New Drug
Mixing of another substance with the New Drug
Error in labelling the New Drug or in the use of the labels designed for the New Drug
Change or deterioration of any lot of the New Drug
F. & D. SECTION C.08.007

THE COST OF DIRECT MAIL

Direct mail, though very important to some companies, is not a major element in the total cost of pharmaceutical marketing. Our 41 companies reported total direct mail expenses of $2,739,000—that is, slightly over 2 per cent of sales revenue, or one cent in the prescription dollar.

Types of Direct Mail

There is a great variation in the type of material which drug companies mail to physicians. Most of it is admittedly promotional—some pieces are just succinct reminders of a use for a particular drug, others are more detailed. However, it also includes extensive brochures about new products, file cards and other literature with the prescribing information covered by the Food and Drug Directorate notice of compliance, and reprints of scientific papers. Sample order cards are mailed by some companies, and there are a few unsolicited mailings of samples of over-the-counter products.

Advantages of Direct Mail

One advantage of direct mail is that it enables companies to provide doctors with exact, and on occasion very extensive, information about particular products. It is also the quickest and most adaptable means of transmitting information, and reaches many physicians who, for one reason or another, are not called on by representatives. Those doctors who do not wish to receive material from any particular company can have their names removed from its mailing list.

MD Attitude to Direct Mail

Some doctors have complained that they receive too much mail from pharmaceutical companies. Surveys taken in Canada show that a general practitioner receives on the average about five pieces of pharmaceutical and medical mail a day. Canadian Mailings Limited conducted continuing studies of the mail of English and French-speaking doctors, which gave the following annual figures for pharmaceutical and medical mail:

	1960	1961	1962	1963
English-speaking General Practitioner	1,825	1,343	1,397	1,332
excluding samples	1,462	1,048	1,134	1,177
French-speaking General Practitioner	2,503	1,766	1,492	1,562
excluding samples	1,990	1,345	1,218	1,327

The general reduction since 1960 in pharmaceutical direct mail is due at least in part to the ending of broadcast sampling. Canadian Mailings Limited discontinued this particular survey in 1964 because the increasing selectivity of mailing techniques made "the average general practitioner" a theoretical, rather than practical, concept.

Related figures developed in the United States show that the American physician receives more than double the direct mail addressed to his Canadian counterpart. The figures for medical and pharmaceutical mail were: 1960 - 4,566; 1961 - 4,089; 1962 - 3,893; 1963 - 3,636. No exactly comparable figures for the United Kingdom exist, but in 1960, a British G.P. received 2,121 pieces of direct mail, in total, compared to 2,147 for an English-speaking G.P. in Canada and 2,946 for a French-speaking G.P. In 1961, the comparative figures were: Britain 1,987; English-speaking G.P. 1,634; French-speaking G.P. 2,170.

The general American and British surveys quoted above both show that about a quarter of physicians regard direct mail as among their most useful sources of information. It is interesting that in Britain manufacturers' literature is rated above Prescribers Journal, the official publication on new drugs.

We know that even doctors who would not commit themselves to this extent do take some time to peruse their mail, and read what catches their interest. More cannot really be expected; only a small proportion is designed for permanent reference. The MRC survey conducted on behalf of MD of Canada reported that 75 per cent of the doctors interviewed said they spent some time with pharmaceutical direct mail--ranging from less than 5 minutes to over 60 minutes a day; 25 per cent said they spent no time reading it. The following figures were also obtained:

26 per cent said direct mail was welcome;
48 per cent said direct mail was unwelcome;
26 per cent were neutral or expressed no opinion.

The fact that there is a general public sentiment against this form of advertising, effective as it is, should be borne in mind when considering these figures. And we still find a quarter of all doctors welcoming a very economical means of providing them with information.

In answer to another, related question:

44 per cent said direct mail was informative;
36 per cent said direct mail was uninformative;
20 per cent were neutral or expressed no opinion.

Increasing Selectivity

One development of some significance in recent years has been the growing selectivity with which companies conduct their direct mail activities. The versatility of the computer promises still further selectivity and refinement of mailing lists in the years ahead. One Toronto

mailing house handles the mechanics of this operation for the majority of pharmaceutical companies.

It reported the following trend:

January 1960		
22 companies made	33 general mailings	
	27 selective mailings	
January 1964		
43 companies made	7 general mailings	
	103 selective mailings	
March 1960		
32 companies made	65 general mailings	
	30 selective mailings	
March 1964		
51 companies made	15 general mailings	
	157 selective mailings	
September 1960		
39 companies made	64 general mailings	
	36 selective mailings	
September 1964		
63 companies made	19 general mailings	
	156 selective mailings	

Selective mailings will be addressed to specialists in a particular field or fields, general practitioners with a known interest in those fields, or, on occasion, to general practitioners as opposed to specialists.

THE COST OF SAMPLING

Regulations Governing Sampling

Sampling in Canada today is subject to quite strict government regulations, which were imposed primarily for safety purposes, following as they did the thalidomide experience. Previously, broadcast sampling was permitted for all drugs except narcotics and controlled drugs—i.e. barbiturates and amphetamines. Under the present regulations, drugs that are available only on prescription may be delivered as samples to a physician on receipt of his personally signed order. The order form must list the name and potency of the drug, the size of the sample, and the date of signature, or of the deliveries involved if there is to be more than one. However, the sampling period covered by one order cannot exceed six months. Also, companies must keep full records of all sample deliveries, available to government inspection, for at least two years.

MD Use of Samples

The value to physicians of the practice of sampling has been shown by the sustained volume of samples distributed under the present regulations. When a new drug comes on the market, it is clearly important for doctors to be able to obtain direct clinical experience of its qualities; they are not going to prescribe any drug extensively without such experience. But sampling is not limited to new drugs; doctors order substantial supplies of established products. A drug may be an excellent medicine for one patient, but prove less suitable for another suffering from an apparently identical condition. There is no doubt that many people would find the cost of drugs substantially higher were it not for the practice of sampling, for using samples initially helps the physician to prescribe the most efficacious drug in each particular case.

Expenditure on Sampling

Our 1963 survey of member companies asked them to report on the cost of samples as well as other promotional activities. For the 41 companies reporting, the total came to $3,939,000— less than 3 per cent of their sales.

At the end of 1964 we sent a questionnaire on the extent and cost of sampling to our members. It was answered by 37 companies, of which 34 stated they distribute samples.

Answering a question whether they were distributing more or less samples since the regulations,

7	companies replied	Less samples
2	" "	Slightly less
4	" "	Less samples, but larger sizes
17	" "	The same amount
4	" "	More samples

In answer to a question on the impact on their costs,

23 companies stated	. . . . .	Costs had increased
11 "	"	Costs had not increased

Specific answers regarding the cost increases referred to either representatives' time or administrative work, or both.

At the time the regulations were enacted, the government indicated that it hoped they would reduce the cost of the drugs concerned as well as provide greater safety. We believe the latter purpose has been well served, but there is every indication that the additional protection to the public has increased the cost of doing business.

TO BE LAID ON THE TABLE OF THE HOUSE OF COMMONS

REPORT OF THE SPECIAL AD HOC COMMITTEE STUDYING MATTERS INVOLVING THE PATENT LICENSING OF DRUG MANUFACTURERS

John N. Crawford, M.D.,
Deputy Minister of National Health.

Tabled by Mr. MacEachen,

May 12, 1966,

Alistair Fraser

Clerk Assistant

July 12th, 1965.

Miss Judy LaMarsh,
Minister,
National Health and Welfare,
Ottawa, Ontario.

Dear Miss LaMarsh,

I am enclosing a report of the Ad Hoc Committee set up to consider problems involved in the compulsory licensing for the manufacture of new drugs. The Committee met on June 24th and again on July 8th, and although the Committee worked under some sense of urgency, a very comprehensive study was made of matters relating to this subject.

You will see that the Committee went beyond the terms of reference for it became obvious to us that the number of new drugs which were produced under compulsory licence was very small compared to the number produced by smaller companies through arrangement with the original developers of the drugs, to some extent under threat of the application for compulsory licence. In the last fifteen years only ten compulsory licences have been granted. Mr. Michel, the Commissioner of Patents was most helpful and spent several hours with us discussing the problems which he encounters in carrying out the regulations. It was obvious that he was most anxious to cooperate with the Food and Drug Directorate and welcomed their help in ensuring the safety of drugs made under a compulsory licence. It is hoped that whatever changes take place in this department, close collaboration can be developed between the Commissioners of Patents and the Food and Drug Directorate. It was a shock to the members of the Committee to find the heavy responsibility put on the Commissioner of Patents. Many of the newer drugs are so complicated in their formulae that part of the products, the isomers, might not be active therapeutically though chemically pure, and some dangerous impurities may not be sufficient in amount, in small samples, to be detected.

Page 2.....

The even greater worry to the Committee was this much larger area of drugs produced under agreement. The Food and Drug Directorate are not informed ahead of time and no inspection is required, although it might occur in the course of time. Samples of the new product prepared by the new company are not now being analysed. The Committee felt that there should be notification of intention to make these agreements. We also felt that annual notification of all drug companies of all drugs that they are producing with specifications would be most helpful.

With regard to the specific conditions listed by Dr. Eloise Jones, you will see that (a) and (c) are covered, that (d) is taken care of in a more logical way. Some companies cannot afford to have a physician, or if they could, would not have a job interesting enough to attract the kind of physician who could fulfill the requirements. The Committee felt it was much better to have available within a matter of a few hours all the information which the physician using the drug might wish to have. With regard to (b), the Committee did not feel that it was practical to demand repetition of clinical trials. At present in Canada we do not have the facilities or personnel to carry out all the trials which are desirable. It is assumed that the first clinical trials were satisfactory and if the Food and Drug Directorate are assured that it is the same chemical and that the potency is equal and no impurities are present and that the prescription form is identical; adequate protection would seem to be provided for the public.

The Committee is greatly indebted to members of the Food and Drug Committee and Mr. Curran for their help. They are tremendously knowledgeable in this field and were most cooperative in giving their time and providing background information for us. The report is respectfully submitted and we all hope that the recommendations may be of some assistance to your department.

Sincerely yours,

Irwin M. Hilliard, M.D., F.R.C.P.(C)

REPORT TO THE MINISTER OF NATIONAL HEALTH AND WELFARE.

The Special Committee appointed by the Minister of National Health and Welfare has the honour to present its report.

On the 14th day of June, your Committee consisting of

Dr. Irwin Hilliard, Chairman,
Physician-in-Chief,
Toronto Western Hospital.

Dr. Charles Gowdey,
Head, Department of Pharmacology,
Western University, London, Ont.

and

Dr. Roger Gaudry,
Rector,
University of Montreal,

was constituted to examine and report on certain matters, involving patent licensing arrangements with respect to drugs.

The Committee met on June 24 and July 8 to consider the above and, in the course of their enquiry, have had the benefit of the views of the Commissioner of Patents and of officers of the Food and Drug Directorate which they found most helpful.

The problem of adequately protecting the public who are using increasing quantities of potent drugs is a constantly changing one. Many of the drugs currently available and much in demand were not even known when the laws re patents and compulsory licensing were formulated. Moreover, modern drugs are usually potent and have important side effects, some predictable from animal tests and clinical trials, but some not predictable, and some not even recognized until many thousands of patients have taken the drug.

Very special legislation is necessary, not only because recent scientific and medical advances have made drugs so much more powerful and dangerous, but also because the public at large is completely unable to realize some of the dangers inherent in the misuse of some of these products. Drugs, therefore, differ greatly from most other commercial products in this very important aspect of safety.

More and more drugs are being produced by synthetic processes of increasing complexity. Because of the number of steps involved and the need for proper care at each intermediate step, it has become essential that adequate quality control procedures be established and carried out at all levels of the manufacture or synthesis of the chemical involved. It is not sufficient any more to perform a simple test on a finished product. In many cases, such tests would not disclose the presence of potentially dangerous by-products or impurities or even chemical isomers which should be removed from the desired material if at all possible. Minor changes in process may perhaps lead to quite different contaminants in finished products and these contaminants may be toxic and may even be missed by routine chemical analysis.

Chemical producers with insufficient staff and technical facilities may either be unaware of or tend to ignore these problems, or may be unable to institute the necessary control procedures which will ensure a standardized product which is safe when used according to direction.

These safeguards have become necessary because over the past few years newer drugs have been discovered which are so active that they affect some of the very fundamental processes of life itself. This means that they must be administered under the most carefully controlled conditions by specialists who are aware that potentially serious side-effects are inseparable from and in many cases may be part of the desired therapeutic effect. It is therefore essential that the prescriber of such drugs be aware that side-effects are likely to occur and that dosages often need to be individually determined. He must also know what is to be done when these side-effects occur, or when an overdose has been taken.

Therefore any company manufacturing such a drug should always be able to provide complete informational material about the product to the medical and paramedical profession; maintain a complete up-to-date file on the properties of and clinical experience obtained with this drug; and be able to supply the necessary information very rapidly to any physician who needs it. This should be available in a matter of hours.

The three main responsibilities associated with the production and the marketing of a potent drug are:

a. The responsibility of the chemical manufacturer to guarantee the utmost quality of the finished bulk chemical.

b. The responsibility of the marketing company to be completely familiar

with all the uses, effects and side-effects of such a drug and to make this information immediately available at all times to the prescribing physician who may require it.

c. The responsibility of the Food and Drug Directorate to ensure that drugs be distributed only when they meet the specifications and standards for such products.

The Committee proposes the following recommendations to deal firstly with a drug in respect of which a compulsory licence under the Patent Act is involved and, secondly, where the holder of a drug patent or a person to whom a notice of compliance has been granted in respect of a drug, proposes to enter into a voluntary arrangement for the manufacture of that drug:

Compulsory Licence

Compulsory licensing for the production of a drug and its implications relevant to the protection of the public were discussed at some length. This subject of licensing was considered important as the Committee feels that patents are valuable in stimulating research and development in the field of drug therapy.

1. A compulsory licence for the preparation or production by chemical or fermentation processes of substances intended for subsequent use in medicines should not be granted unless there is first furnished to the Commissioner of Patents a favourable report or certification by the Director of the Food and Drug Directorate on the competency of the applicant for such licence to manufacture or produce such substance, including adequacy of manufacturing facilities and

controls as required by the Food and Drug Regulations.

2. The necessity for close collaboration between the Commissioner of Patents and the Food and Drug Directorate who are responsible for the safety of the finished product is obvious and the Committee were impressed with the willingness of the Commissioner of Patents to work closely with the Food and Drug Directorate.

Before a licensee to whom a compulsory licence has been issued or any manufacturer under that licence releases the drug in dosage form for sale or distribution

(a) he shall furnish to the Director of the Food and Drug Directorate a sample of such drug in dosage form and submit evidence that it has been manufactured in conformity with and meets the requirements of the Food and Drugs Act and Regulations.

(b) he shall also furnish to the Director copies of any labels and promotional literature proposed to be used in connection with the sale or distribution of the drug, and

(c) there shall have been an inspection of his premises and a report received by the Director indicating satisfactory compliance with the requirements of Section C.01.051 of the Food and Drug Regulations.

Voluntary Licence

In reviewing the number of compulsory licenses granted in the last 15 years (approximately 10) it became apparent to the Committee that another

large area of concern should be the problem of voluntary arrangements made by the company holding the patent for the drug with other companies, sometimes possibly under threat of an application for a compulsory licence. Up to the present time the Food and Drug Directorate have not always had prior notification of such arrangements.

Whenever a person who is the holder of a drug patent or who is a person to whom a notice of compliance respecting a drug has been issued pursuant to the New Drug Regulations, enters into a voluntary arrangement with another person to manufacture or produce that drug in Canada, he shall first notify the Director of the Food and Drug Directorate giving the name of the proposed manufacturer, the name of the drug, and the address of the premises where such drug will be manufactured or produced.

A manufacturer of a drug pursuant to an arrangement as referred to in paragraph 3, shall, before releasing the drug in dosage form for sale or distribution, meet the requirements of paragraph 2, namely:

(a) furnish to the Food and Drug Directorate a sample of such drug in dosage form and submit evidence that it has been manufactured in conformity with and meets the requirements of the Food and Drugs Act and Regulations, and

(b) submit copies of labels and promotional literature proposed to be used in connection with the sale or distribution of that drug, and

(c) submit evidence that an inspection has been made of his premises and a report received by the Director indicating satisfactory compliance with the requirements of Section C.01.051 of the Food and Drug Regulations.

New Drugs

The Committee felt that there was adequate protection of the public through the present regulations, with regard to new drugs. The following recommendations, however, were made to broaden the scope of the term:

That the definition of a new drug be amended to include a drug not currently in new drug status if it is to be manufactured or produced by a method or process that is substantially different from the method or process currently being used in Canada; or if with prolonged use, new or more serious or more frequent side effects, develop.

That if any drug, made subject to a compulsory licence or voluntary arrangement in the opinion of the Food and Drug Directorate or the Canadian Drug Advisory Committee or any sub-committee thereof, requires special manufacturing facilities or controls or further testing, which may include clinical testing, provision be made in the New Drug Regulations that it be dealt with as a new drug.

Availability of Information

7. While it would be desirable for a physician to have ready access to a responsible medical officer on the staff of a drug manufacturer, this may not be feasible or even necessary under all circumstances. The Committee feels that responsible manufacturers will use their best judgment in this regard but whether or not there is a duly qualified medical practitioner available, it recommends that no manufacturer shall market any drug unless he has available a product brochure containing

complete information on the indications, contra-indications, precautions, dosage and side-effects, as well as a resume of the pharmacological and clinical studies carried out on that drug and that such brochure be furnished, on request, to any physician, dentist, veterinary surgeon or pharmacist registered and entitled to practise his profession in a province of Canada.

In studying the problem of compulsory licensing of drugs and voluntary agreements, the Committee noted certain other areas of general concern and would make three further recommendations.

Notification

8. That all drug manufacturers in Canada be required regularly to notify the Food and Drug Directorate of their name, address, names (trade and official) of their products, and any other pertinent information. (The Committee understood that this is already under consideration).

Identification

9. That companies marketing drugs use an identification mark on the finished product as well as recording the lot number on the container.

Imported Drugs

10. Distributors receiving bulk, semi-finished or finished drug products from outside Canada must provide satisfactory evidence of testing of the imported drug with regard to identity, purity, and potency before marketing such drugs in Canada.

Dated at Ottawa,

this 8th day of

July, 1965.

Respectfully submitted.

Roger Gaudry

Charles Gowdey

Irwin Hilliard.
(Chairman)

"QUALITY OF DRUGS"

(An analysis of the section of the Hall Commission report entitled "Quality of Drugs", pp. 366-370.)

The Section discusses the powers and activities of the Food and Drug Directorate relating to the quality of drugs sold in Canada. In so doing, it overstates the existing administrative and legal protection of drug quality——as opposed to the protection provided through the procedures of reputable brand-name manufacturers. It understates the necessary expansion of existing inspection forces to "adequately test and check drugs in Canada," in particular through the misquotation of Dr. C.A. Morrell.

The following exchange between Dr. Morrell and J.A. Macaluso, M.P., member of the Special Committee of the Commons on Food and Drugs, appears pertinent in this connection:

> Dr. Morrell: ...I am loath to have people say that a drug is guaranteed by the Food and Drug Directorate. I do not see how we can guarantee it. There are many subtleties, and we have not the facilities to detect differences.
>
> Mr. Macaluso: I do not mean the safety of the drug as to its side effects.
>
> Dr. Morrell: But you cannot put "government approved" on a drug.
>
> (Minutes of Proceedings p. 158)

The errors and misconceptions of the "Quality of Drugs" section of the Hall Commission report are reviewed against the definition above of the potential and the limits of government inspection.

Quality Control and Potency

On page 369, the Hall Commission report refers to what it calls "at least two hopeful elements in the situation." For both of these, it quotes from Dr. Morrell's evidence before the Restrictive Trade Practices Commission.

The first one is the fact that, "quality control elements for any particular company depend upon the number of products being manufactured and the danger or potency inherent in them." This is undeniable, provided the standard is high enough to ensure therapeutic quality and safety.. However, since it is the cost of the more complex drugs of greater potency and toxicity that is chiefly under discussion, the relevance of the argument is not immediately apparent.

Staff Needed by FDD

The second "hopeful element" is explained in the report as follows: "Dr. Morrell further expressed the opinion that in order to adequately test and check drugs in Canada the Food and Drug Directorate would have to triple its staff of inspectors and laboratory personnel." This appears a gloss upon the following exchange before the Restrictive Trade Practices Commission (pp. 141-143):

Mr. Hume (counsel to the PMAC): Is it your opinion you have sufficient inspectors and lab people to adequately test and check drugs in Canada?

Dr. Morrell: No

Mr. Hume: Could you indicate whether or not this number you think should be doubled or tripled knowing the population and the demands on your staff...?

Dr. Morrell: Oh maybe two or three times as many as we now have, perhaps three times.

Mr. Hume: ...I wonder if you could indicate to the Commission what you would consider to be an adequate staff to be able to protect the public against any drug which might be improper, whether generic name or otherwise?

Dr. Morrell: You are giving us quite a job to do. I don't know the Food and Drug Directorate should act as a control laboratory for all people who want to manufacture pharmaceuticals in Canada. I don't think that is our function. We are acting as a police agency, I believe. If you want me to analyse every batch of a drug or pharmaceutical sold in Canada, I think it would be an astonishing number. I believe we would need——when I said three times the number of inspectors I wasn't speaking of that kind of job.

In this connection it is significant that the Special Committee on Food and Drugs of the House of Commons recommends that the staff of the Food and Drug Directorate be doubled to enable it to handle effectively its present responsibilities. (Proceedings p. 518)

Extent of FDD Inspection in Canada

The Hall Commission states that about 450 inspections of drug plants are carried out in a year by the Food and Drug Directorate, and that on one occasion the Directorate sent an inspector to Italy.

The figure actually given by Dr. Morrell to the RTPC was "300 or 400." (RTPC report p. 156) Mr. B.S. Mackasey, M.P. asked about the number of inspections when Dr. Morrell appeared before the Special Committee on Food and Drugs of the Commons.

Mr. Mackasey: My second question is: How many drug businesses have been inspected by the food and drug offices?

Dr. Morrell: We do it by calendar year. If I could give you the number that were inspected in 1963, would that satisfy you?

Mr. Mackasey: That would be ideal.

Dr. Morrell: The quality control regulations which are now in the Regulations of the Food and Drugs Act were introduced in March 1963, and during the calendar year 1963 there were 183 plants inspected.

Mr. Mackasey: With the personnel at your disposal, is it possible to cover all these people at least once a year?

Dr. Morrell: You mean the 485 manufacturers? No, it would not.

Mr. Mackasey: What increase in personnel do you think you would need to do this job adequately, or would you say that once a year is too frequent?

Dr. Morrell: It is not adequate in my opinion, Mr. Mackasey.

(Proceedings, p. 142)

Extent of FDD Inspection Overseas

Later in the same session of the committee, Mr. Mackasey asked the following question: "How many inspections of drug manufacturers facilities outside of Canada which supply drugs to Canadian manufacturers have been carried on by inspectors of the Food and Drug Directorate?"

Dr. Morrell: We have done none so far in the pharmaceutical field. I want to be sure that when we send an inspector to Europe he really knows his business, because I think he would have to. In terms of other drugs under the Food and Drugs Act, the biologics for example, we have an inspection scheme.

(Proceedings, p. 145)

No Notice of Compliance for Established Drugs

Certain other statements in the "Quality of Drugs" section also call for careful analysis.

At the foot of page 366 it is stated: "Not only every new drug but every new preparation of it (i.e. by another supplier) must be cleared by the Food and Drug Directorate. This requires a new submission and a new notice of compliance." This is true only of those drugs or preparations which come within the Directorate classification of "a new drug." With established drugs, a second supplier can put an imitative product on the market without obtaining a notice of compliance. The implications of this were made clear by Dr. Eloise Jones, M.P. in her statement in the House of Commons on June 4, 1965 (Hansard pp.1977-8).

Confusion Between Federal and Provincial Requirements

On pages 367 and 368 a number of statements are made that are also only partially true:

"The provincial pharmacy acts supplement the Food and Drugs Act in providing for a listing of drugs which may be sold only on prescription." There is considerable variance between the schedules of the various provincial acts, several of which are badly out of date, and between them and the Federal schedules. The result of this is more likely to be confusion than greater safety——unless it be assumed that the Federal schedules are inadequate.

Limits of Label Information

"There are specific regulations under the Food and Drugs Act also, pertaining to the labelling of drugs, designed to inform the physician, the druggist and the public about their safe and proper use." This gives the impression that all drugs and all labels are covered by such regulations, and that labels are a source of information for the general public. This may be true in its broadest sense. However, the specific regulation requires that the label bear "adequate direction for use". This will range from detailed dosage information, together with such mandatory cautionary statements as may be required by the regulations, or may be considered necessary by the manufacturer, for a drug intended to be sold directly to the public, to a simple statement such as "to be used only as directed by the physician" for a drug available only on prescription. It is not intended that every label of every drug carry information designed to inform the physician, the druggist and the public all at the same time.

Availability of Medication

"Among the basic qualities demanded by the law are that... the medication must be contained in such a way as to be wholly available to the consumer of the drug." There is no general requirement to this effect. However, C.01.012 does lay down a regulation

with regard to timed release products to the effect that the manufacturer shall demonstrate that the drug is released and available as claimed when determined by an acceptable method.

FDD Inspection of Imported Drugs

"Imported drugs are also inspected on a sampling basis. In those custom ports where there are no drug inspectors, the Food and Drug Directorate is notified by customs inspectors of shipments of drugs coming into the country. These shipments are held until a release is obtained from the Food and Drug Directorate." This statement is taken from the testimony to the RTPC of Dr. Morrell. However, Mr. F.N. MacLeod of the Department of Justice then went on to ask Dr. Morrell: "Is it a fact then that your Directorate is notified of every importation of drugs into this country?" And Dr. Morrell answered, "No, I would not say it was a fact. A good many of them, but certainly not all of them." Dr. Morrell then went on to explain the reasons for this (RTPC report p. 162). In addition, the paragraph in the Hall Commission report gives the impression that a Directorate release is made only after a full analysis of the shipment in question. In answer to Mr. MacLeod, Dr. Morrell pointed out that samples were taken only from selected shipments.

Interesting in this connection is the exchange that occurred between Dr. Morrell and Mr. Macaluso at the hearings of the Special Committee of the Commons on Food and Drugs. Referring to a distributor in Hamilton who imported drugs from the West Indies, "and has run into some trouble with the Food and Drug Directorate," Mr. Macaluso asked: "Is there any type of inspection carried on in regard to drugs coming from the West Indies or from Jamaica, and are they checked by the food and drug inspectors when they come through customs?"

Dr. Morrell: We would check them if we have a laboratory man available. We do not check all of it. Again, we are short of staff.

Mr. Macaluso: You agree that in a case like that there is no analytical control or inspection and there is therefore a danger there?

Dr. Morrell: Yes there is a danger there. (Proceedings pp.145-6)

Concerned about "drugs that are imported into Canada and distributed without further processing," the Special Committee of the Commons made the following recommendation:

> "that inspection of quality control methods here and abroad should be carried out by the Food and Drug Directorate. If felt necessary by the Food and Drug Directorate this quality control check should be carried out by any importer before the drug is released in Canada. If this inspection is not carried out or does not meet our standards the imported drug would not be released in Canada." (Proceedings p. 515)

It should be noted that such inspection would relate only to the existence of satisfactory methods of quality control; it would not be a government guarantee of the quality of specific batches or products.

Responsibilities of Government and Manufacturer

On page 370, the Commission uses the testimony of Professor J.L. Summers of the University of Saskatchewan to support its claim that FDD inspectors could test and check drugs made abroad through inspection. Here again the extract from the testimony distorts the point that Professor Summers was actually making. (RTPC hearings p. 2254)

J.J. Frawley: (Counsel for the Province of Alberta):...What would be the difficulty about the Food and Drug Directorate undertaking this responsibility which they don't undertake and putting the stamp of approval on non-proprietary drugs so that it could go out without those disabilities you have called to our attention?

Prof. Summers: I don't think that is a function of Government. It is the responsibility of the individual manufacturer. It is the responsibility of Government to set such standards as it deems are adequate to protect the people of this country and to see that the manufacturer observes his obligations and responsibilities. Now, this can be done by inspecting these plants. No knowledgeable person in the field of pharmacy could walk into a plant and spend a day with them and not know more and learn more about the quality of the product which they produce than analytically, by testing they could learn in five years. It is the products that are produced...

Mr. Frawley: Let us be very...

Prof. Summers: You can't inspect quality into the product. It must be built in by knowledge and ability.

This categorical statement by Professor Summers, now president of the Canadian Pharmaceutical Association, would seem to best sum up the argument against the concept promoted in the "Quality of Drugs" section of the Hall Commission report. Government cannot inspect quality into any product, but there is much for Government to do through the inspection and, if feasible, registration of manufacturers to protect the Canadian consumer. Under present circumstances, the Food and Drug Directorate is unable to employ sufficient personnel of suitable calibre to carry out this latter task. Here is an area where immediate action is required—and where practical results can be achieved. To seek less is to fail the Canadian people; to claim more is to mislead them.

WHAT IS A GENERIC EQUIVALENT?

From American Professional Pharmacist

By Max S. Sadove, B.S. in Pharmacy, M.D.,
and Ronald Rosenberg, M.D., Floyd Heller, M.D.,
Morton Shulman, M.D.

Having degrees in Pharmacy and Medicine — in addition to being involved in medical practice, teaching, and research & development — we have a real and often vital problem in the area of: What is a generic equivalent?

The answer to this question is especially important in that our budgets are fixed, relatively small, and frequently "in the red." Economy is a very important part of our mission, yet we must get uniform, dependable, and predictable drug results with a minimum of side actions. Basically, we represent a research and clinical department whose primary function is the care of patients (anesthesiologic), teaching, and research — with special interest in pre-operative, operative, and post-operative care.

With respect to drugs, no income accrues to individuals or the department. Any savings on drugs can be used for any of our pet projects or for research, instruments, and equipment. Economics, scientific truth, and clinical results are all vital as they relate to drugs. "Generic equivalency" is a daily problem to us.

BACKGROUND

Over a period of about 2 decades, we have been using various drugs daily. On many of these, we have performed the early laboratory testing or clinical and laboratory testing. We have been an active department in clinical and laboratory evaluation. Then, subsequently, we make use of the drugs. We have studied competitive, generic equivalents, and similar drugs.

In our teachings, we use the generic terms and, where logical and efficient, we employ the generic concept. It is difficult to teach this concept. Even those dedicated to the principle find it hard and unwieldly — and also confusing and foolish at times — because everyone knows a drug by a trade name and does not know what we are talking about when we use the generic term for the drug.

EQUIVALENTS?

The principal problem we have, however, is to know what "generic equivalent" really means; also, when are 2 generic equivalents pharmacologic equivalents or "clinically effective" equivalents?

"Generic equivalents" are a continuous problem for us economically, scientifically, and socially. We have a pharmacy college as part of our structure — and personnel who are strongly dedicated to the philosophy of the truth of the "generic equivalent story."

Therefore, we will discuss our views with respect to "generic equivalents" — in that it might help others reach a conclusion and get closer to the truth. Some of our experiences and thoughts — presented below — explain why we cannot reach a quick and easy decision on this problem of what are generic equivalents:

1. SALT

In the early days of erythromycin, we were given 2 products made by 2 of the leading pharmaceutical companies. These were to be used in our recovery room; we were also to observe any local changes as well as systemic reactions. One of the 2 erythromycin products was extremely irritating. There were many violent complaints from patients and nurses. The product that irritated was finally changed from one salt form to another. The irritancy immediately fell to a very satisfactory level.

Thus, it makes a real and definite difference to us which particular salt of a drug we get. It can change many, many factors — not the least of which are irritancy, patient tolerance, absorption, etc. If we ask for a specific drug in a specific salt form, it would be unwise to have another salt form substituted — unless one knows what difference this may make in its tolerance, uptake, distribution, destruction, etc.

These 24 Factors Can Markedly Alter the Pharmacologic Action of a Drug

1. Size of crystal or particle.
2. Form of the agent — solution vs. salt.
3. Vehicle.
4. Coatings.
5. Degree of hydration of crystal or addition of de-hydrating substances to package.
6. Diluent.
7. Purity — type & number of impurities.
8. Viscosity.
9. pH.
10. Sustained release forms.
11. Enteric coating.
12. Solubility.
13. Vehicle or base.
14. Container — stopper, type of glass, whether or not glass is pre-heated or impervious.
15. Package dating.
16. Quantity of active ingredient.
17. Contaminants.
18. Allergenic substances.
19. Irritation.
20. Melting point.
21. Toxicity.
22. Surface tension.
23. Storage factors.
24. Flavoring & Coloring agents.

2. VEHICLE

We have, on several occasions, used a soluble barbiturate of

essentially the same primary molecule, but in different vehicles. In many instances, the ease of pharmaceutically mixing "like drugs" prior to injection was markedly changed. The shelf life was markedly altered.

In one instance, the less expensive drug became more expensive, because of the amount that had to be discarded owing to changes in physical characteristics. There are many procedures in manufacturing trademarked products that add to their pharmaceutical stability and shelf life. It can mean that a different vehicle product is not the same as far as effect and appearance are concerned.

Thus, when are there real savings on 2 similar products with different vehicles? We really don't know without a period of testing.

3. pH

We have studied many different local anesthetics. We have found in testing them on animals and on ourselves that there is a really significant difference in local irritancy, onset, and duration — dependent upon the buffering agents. This same factor definitely affects many other drugs.

Thus, to substitute one generic equivalent drug for another, one must be sure that the hydrogen ion concentration and the amount & type of buffering is identical — or else one is getting an entirely different drug effect. Though presumably generically equivalent, the drugs may be pharmacologically and clinically different. The effect of pH on stability, compatibility, ionization, etc., is too well known to discuss, but it is frequently forgotten.

4. CONTAINERS

Containers can make a real difference in the effect of a drug. Several years ago, we were doing clinical and laboratory evaluation of a drug and were quite pleased with its effects. After a while, we felt that it would be more efficient to have 30-cc. vials of the drug, rather than 10-cc. ampules. Within days after we had received the vials, we changed our opinion of the drug. It had been non-irritating when injected in the initial study — now, it irritated. The manufacturer was at a loss, at first, as to the cause. Finally, the cause was determined. The vials were stoppered with new closures that were high in heavy metal content. This heavy metal was being leeched from the stopper into the solution, causing the tremendous increase in irritancy.

The type of glass used can also make a major difference in many solutions. Thus, differences in stoppers, glass, dehydrating agents, filling gas, etc. — can all alter the biologic difference in a drug. Many of these differences are too obvious to discuss with a professional group like pharmacists.

5. VEHICLES

Vehicles make a tremendous difference in many drugs. In topically-active drugs—such as eye solutions, solutions for nose & throat ... and also in intravenous solutions, intramuscular solutions or suspensions —the difference can be such as to render the drug completely different pharmacologically; in fact, different vehicles can change the drug from a useful drug to a very dangerous drug. Vehicle changes alter stability, compatibility, irritancy, toxicity, allergenicity, and pharmacologic effect.

On one occasion, the change in vehicle of a test drug endangered the life of one of the authors in that a thrombophlebitis developed in the deep veins of his arm which ascended well into the axilla. This caused the consulting surgeon to contemplate ligation of a subclavian vein. Prior injection of the same drug—but with a different vehicle—had not produced untoward results. Of course, this is not significant from a proof standpoint, but would be sufficient from a clinical standpoint to frighten one of the authors from ever having that drug used on himself in any form of testing. Then, testing of 2 solutions demonstrated that the author reacted to one lecithin solution—not to another.

Thus, one must realize that the changing of a vehicle can alter viscosity, compatibility, stability, irritancy, allergenicity, etc.—so that this factor must be known if one is to substitute one "generic equivalent" for another.

6. STABILIZING AGENTS

Stabilizing substances can certainly make a marked difference in compatibility, irritancy, duration of action, shelf life, dosage, and even action of a drug. The fact that a therapeutic agent has been placed in equal quantity in 2 products does not mean that there will be equal availability of the primary agent after a given time. Nor does it mean that the rate of absorption or availability of the drug will be the same for the 2 products.

This difference may be even more marked once a product has been opened, as is the case in a multiple-dose vial. In some instances, we cannot use one form of a drug—such as a local anesthetic—because the antibacterial agent or the stabilizer is contra-indicated. For example, when we use local anesthetics for epidural anestnesia, we must be sure that there is nothing in the preparation that can injure the spinal cord. It is quite possible that we may inadvertently perform a puncture of the dura while doing an epidural block—also that the solution may be unnecessarily irritating to the dura, but not to the peripheral tissues.

It becomes obvious that the preservative, antibacterial agent, stabilizing agent, anti-oxidative agent, etc., are important in the final comparison of 2 solutions, because they can markedly alter the pharmacologic effects of the principal ingredient. In many products, this information is not available and, thus, we do not know whether one "generic equivalent" may be used for another.

7. PACKAGING

The packaging of a product may make a real difference in the economy and use——as well as usefulness——of 2 identical products. Frequently, in the purchase of a volatile agent, for example, even the same company's product at 2 different periods may be so packaged as to reduce loss by 25%.

On several occasions on foreign trips, we have encountered diethyl ether that was apparently similarly packaged to American products, but on inspection many of the packages were partially empty or completely empty.

8. CONTROLS

At one time, we made our own intravenous fluids. Extreme care was taken to make these so that they would be quality products. Yet, our pyrogenic and allergic reactions were quite frequent as compared to the manufacturer's product line we now use. Generically, they were equivalent; actually, they were tremendously different.

With the present line of intravenous fluids, we find that allergic and pyrogenic reactions are almost non-existent.

9. CONTAMINANTS

A few years ago, we experienced a failure in a series of reducing regulators on nitrous oxide tanks. This was the first and only time this had happened in a period of over 15 years. Study revealed that a new contract had gone to a minor company, because they had been "low bidders" for our gas contract. It was necessary to stop using the gases of the low-bid company.

In fact, we fear all low bids when they are sharply lower than the bids of the so-called "good companies." What short cuts——what changes---have occurred to make possible the reduced price? The specifications theoretically are the same for all companies and their products, but practically the products can be very different. Sometimes a so-called minor contaminant can make a major difference in 2 products. In many instances, manufacturing know-how——gained by long experience——makes the difference in product quality.

DESIRABLE, BUT . . .

The desire to get the same therapeutic effect for less cost is a very reasonable one, but where can one find the data that would enable one to make this judgment? In general, it can be stated that this information is usually available only to a very few people with large laboratories, plenty of time, and a great deal of experience. Even the skilled pharmacologist frequently cannot pinpoint the difference.

Careful laboratory testing frequently does not reveal the difference between "generic equivalents" that are clinically very different. For example, tetracaine has been purchased by certain government agencies to replace Pontocaine. Generically, the products are equal, but clinically the complaints — involving shorter duration, greater number of failures, shorter shelf life, and crystal formation — were very frequent about the tetracaine. It was never revealed to the anesthesiologists involved why this was so.

Many of the anesthesiologists did everything in their power to obtain the Pontocaine solution they had been using before the material from another company had been substituted. Many of these people did not know of the same difficulties in other locations.

Did the difference in cost justify this change to a generic product from the branded product? In retrospect, it is obvious that the answer is no, but can this kind of error be prevented? We really don't know how it can. The specifications of the 2 products were identical. The clinical results were entirely different!

There are many factors which determine the onset, duration, side reactions, and principal action of a drug. In many instances, it is physically impossible to compare 2 similar products without extensive, carefully-controlled laboratory and clinical trials. Though it is admirable to keep the cost of drugs to a minimum and it is admirable to know and prescribe drugs generically, the generically-similar product exerts, in many instances, a very different reaction from the one anticipated.

It is practically impossible for one not skilled in the area of clinical pharmacology to know what is — and what is not — a real "equivalent."

Above all, the lack of available data would preclude substitution without prior equation of the many factors which could materially alter apparent equivalency.

A FABLE

Our conclusion is that generic equivalency is frequently a fable without basis in fact; chemical equivalency of the primary agent or agents is not necessarily clinical nor pharmacologic equivalency.

PHARMACARE

PHARMACARE, a service program with a payment direct to the provider of service rather than a reimbursement program, is directed and operated by members of the profession of Pharmacy. It embodies guaranteed financing, guaranteed service and guaranteed fee costs with charges influenced only by the cost of the tangible ingredients of prescriptions. It may be operated as a separate entity or integrated with programs providing for other health services.

The PHARMACARE program is specifically designed to meet modern desires for a completely adequate method of financing the individual's requirements in relation to drug therapy and is in keeping with philosophies expressed by private citizens, management, labour, governments and the professions. Pharmacy's views are expressed in the CPhA Statement of Policy Relative to Health Insurance Plans. The Canadian Chamber of Commerce Statement of Policy, 1965, states: "In a free society, the individual has the primary responsibility to make provision for and pay the cost of health care for himself...budgeting for adequate coverage...with voluntary service, indemnity plans and the contribution of government to assist those who are unable to provide for themselves." Organized labour has repeatedly stated that health service plans are a desirable fringe benefit. Canada's Royal Commission on Health Services emphasizes "the individual's reponsibility for personal health...to the extent of the individual's capabilities"; belief "that an individual family should not have to bear alone the full cost of risks..."; the rationale of health insurance which embodies the application of averages for the relief of millions...and the desirability of "necessary legislative, organizational and financial decisions to make all the fruits of the health sciences available to all our residents without hindrance of any kind." Many governments — federal, provincial and local — have made pronouncements of varying degrees of specificity. PHARMACARE is adaptable to most political philosophies in that it enables the individual to assume a responsibility to provide for his pharmaceutical therapy needs while enabling the group as a whole to share responsibility to thus ensure that the services are available at a cost within every individual's ability to pay.

Features:

The PHARMACARE Plan embodies three responsibility phases, namely: a period of individual financial responsibility; the sharing of financial responsibility (co-insurance); and thereafter, full coverage ('fire insurance').

The Plan:

Health insurance, and particularly that having to do with the insuring of first class pharmaceutical services provided by community pharmacies has been the subject of many years of review and study by the pharmacists of Canada. PHARMACARE is the result of intensified study during the past eighteen months.

1. Subscribers

No restrictions as to age, condition of health, occupation, geographic location.

Groups of 5 or more (i.e., recognizable groups of all types, including labour, management, professional and civic, except as organized for the purpose of obtaining health insurance and except health groups).

Welfare and medically indigent categories for whom a central authority assumes financial responsibility.

Individuals who move out of a group contract or outside of the dependent age.

Non-group individuals, in due course, according to the experience of the Plan.

2. Benefits

All pharmaceutical services prescribed by medical and dental practitioners --- a few exceptions such as patent medicines, accessories, first aid supplies, etc. --- all procedures in keeping with all usual and legal practices normally followed by the professions relative to drug therapy (i.e., prescribing habits, repeat prescriptions, long term medication).

3. Coverage

Combines features of prepayment and insurance -- no limit as to maximum relative to pre-existing medical history and/or illness situations.

For single subscriber, after first $10 (family $20) PHARMACARE assumes 80% of next $50 (family $100) with subscriber paying only 20% to the provider of service, and thereafter, subscriber is 100% insured for 12-month benefit period.

Features

(a) Enables subscriber to budget completely to a maximum amount for prescription services;
(b) Keeps insurance premium cost to a very reasonable level;
(c) Subscriber individually responsible only for normal, average expenditure;
(d) Subscriber's participation during co-insurance phase provides for sharing with others of his above-average expenditures;
(e) Deductible and co-insurance phases deter over-demand and/or wastage;
(f) Full insurance coverage protects against abnormal and catastrophic situations.

4. Benefits period

Any 12-month period beginning from the subscriber's choice of date of first prescription service following effective date of contract.

5. Identification of subscriber

(a) Pocket card for reference purposes only;

(b) Personalized book of pre-punched cards serving as subscriber's receipt and cumulative record; as the pharmacist's record; and as an accounting form.

6. Payment for services

(a) Direct to providers of service, namely, retail pharmacies operating under the pharmaceutical legislation of the province --- amounts according to a negotiated contractual agreement between the Company and a representative pharmacist organization; on basis of cost of ingredient plus a professional fee;
(b) Reimbursement to subscribers provided for where services obtained in areas where no member-pharmacies.

7. Premiums

(a) Group rates, annual payment structure, single subscriber and family rates (at 3X single);
(b) Pay-direct rates for subscribers previously in a group at slightly higher premium;
(c) When sold to non-group individuals, higher rate structure required.

Financial Resources:

PHARMACARE is organized as a non-profit Company capitalized by the purchase of shares and debentures by members of the profession of Pharmacy who are the providers of the services.

The ability of the Company to provide services is guaranteed by the profession of Pharmacy to the extent that if the financial resources of the Company prove inadequate, the pharmacists will agree to accept reduced fees and, where agreement is obtained, the manufacturers of the ingredients will pay in an equal amount.

Policy Direction, Sales and Administration:

Policy will rest with a Board of Directors which, in addition to the pharmaceutical profession, may include lay persons such as employers and employees and others representative of subscribing groups.

Sales and administration activities shall be the direct responsibility of the Company through its own staff and facilities or through the utilization of those of an organization with which it enters into an agreement for such purpose.

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Abbott Laboratories Ltd.

Ames Company of Canada, Ltd.

Anca Laboratories.

Arlington-Funk Laboratories.

Astra Pharmaceuticals (Canada) Ltd.

Ayerst Laboratories.

Baxter Laboratories of Canada Ltd.

Bristol Laboratories of Canada Ltd.

The British Drug Houses (Canada) Ltd.

Burroughs Wellcome & Co. (Canada) Ltd.

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FBA Pharmaceuticals Ltd.

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